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Symposium on Mitral Regurgitation (Part III)*

Mitral Regurgitation†

A Group of Surgical Problems

DWIGHT E. HARKEN, M.D., F.A.C.C.

Boston, Massachusetts

THE MANY surgical procedures that have been offered to palliate mitral regurgitation bespeak dissatisfaction. Intrinsic ball, bottle and spindle baffles, transorificial stents, pericardial slings, leaflet suture, commissural plication, circumclusion, and other procedures have attractive but limiting features. Indeed, this protean disease is now being palliated, but ultimate correction of all forms will require a variety of procedures. Some of these procedures are available, other definitive operations can be predicted.

This discussion will deal with certain general, then specific morphologic and hemodynamic features of mitral regurgitation.

BASIC MORPHOLOGIC AND HEMODYNAMIC CONSIDERATIONS

The normal position of the mitral annulus is just within the upper portion of the left ventricle. Closure of this valve is accomplished by the reduction in annulus size and by relaxation of the leaflet edges as the chordae tendineae are relaxed in systole. Leaflet margin closure is further secured by the twisting motion of the ventricle and torsion of the chordae tendineae.

The leaflets are in direct continuity not only with the annulus but the auricular endocardium. Even if initially uniform, a regurgitating systolic jet impinges most forcibly on the suprajacent auricular wall. This pulsion dilates the auricle, displacing the annulus over the ventricular rim by traction. This migration represents *direct herniation* of the valve complex. It can also be appreciated that as the valve complex is drawn upward over the ventricular rim, the effective component of leaflets posteriorly is reduced and local incompetence is increased. This local posterior increment in regurgitation further increases the jet and further aggravates the direct herniation and shortening of the leaflets. This is one of the many features of "self aggravation" of mitral incompetence. It also explains the greater insufficiency posteriorly and postero-

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† From the Departments of Surgery, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Massachusetts. This study was supported in part by Grant H2419 (c) of the National Heart Institute.

medially. As the valve complex moves upward, the chordae tendineae are drawn taut and interfere with leaflet closure. Similarly, compensatory dilatation of the ventricle not only enlarges the annulus but increases the tension on the chordae tendineae; both increase incompetence.

Compensatory Mechanisms in Mitral Regurgitation: The gradient in systole between the left ventricle and the left auricle is much greater than that between the left ventricle and the aorta; thus regurgitation is favored over forward flow. In order to maintain cardiac output, a larger volume of blood (equal to the combined aortic output and the regurgitant jet) must flow from the auricle into the ventricle during each diastolic period. This large forward flow is at the considerable hemodynamic disadvantage of a low auriculo-ventricular diastolic gradient but high systolic ventriculo-auricular gradient. Two principal mechanisms of compensating for this unfavorable dynamic situation exist. *The first is that the slower flow from auricle to ventricle during diastole may take place over a longer period of time.* Diastole must be substantially longer than systole. The limitations of such compensation in tachycardia are apparent. A given degree of incompetence will obviously be tolerated better at slow rates than rapid rates, for systole shortens little in tachycardia, the time loss is in diastole. *The second mechanism by which this compensation is maintained is through a change in the size of the mitral orifice.* The larger volume of blood traveling at a low velocity during diastole advances through a larger orifice than does the regurgitant jet in systole. This depends primarily upon the maintenance of leaflet mobility and to a lesser degree upon the partial occlusion of the orifice by ventricular contraction in systole. Unfortunately, a patient with fixed calcific leaflets or sutured leaflets loses this important form of compensation.

Morphologic Patterns in Mitral Regurgitation: The hemodynamic considerations above make some of the morphologic characteristics easier to understand. The reason for the greater area of incompetence posteriorly is clarified. The usual illustration of the mitral valve surface does not represent the upward herniation of the valve complex posteriorly and it does not indicate the leaflet limitation by chordae tendineae drawn taut by the upward migration of the leaflet complex and papillary muscles displaced downward by ventricular dilatation. The five general morphologic patterns do, however, serve some purpose in understanding the disease.

Type I embraces scarred and contracted leaflets, incompetent through *absolute deficiency of substance.*

Type II consists of leaflets that cannot come together completely through dilatation of the annulus, or the *relative deficiency of substance;* e.g., secondary to myocardial disease and ventricular dilatation, or dilatation incident to aortic valve disease. This form often follows and is combined with Type I.

Type III is a group of primarily stenotic orifices *facing the outflow tract.* Here the stenotic funnel scoops up blood in systole and regurgitation occurs. Occasionally, this insufficiency can be corrected by correcting the stenosis.

Type IV is a group with *poor coaptation* due to heavily calcific leaflets. There may be a greater or lesser loss of substance. When the stenotic component is important it can be relieved surgically and ofttimes with careful leaflet mobilization, particularly of the posteromedial commissure, the regurgitant jet is less.

Type V is a common form of *combined stenosis and insufficiency.* Here the noncalcific, incompetent area lies posteromedially and the stenotic anterior bridge is often calcified. Whether surgery should be directed at the incompetence, the stenosis, or both is a function of the degree of each and the quality of surgical correction. Occasionally this "*combined form*" has a very narrow anterior bridge of stenosis which if divided allows the whole annulus to open widely as a horseshoe with lethal incompetence.

Having carefully placed all forms of insufficiency in five groups, it is again emphasized that an infinite variety of combinations of these forms exist.

Basic Surgical Considerations

An interesting hemodynamic experiment can be conducted at the operating table as the surgeon palpates a regurgitant jet with the exploring finger. The greatest jet is generally located at the posteromedial commissural area. With

the index finger on the left hand outside the heart and above the ventricular rim, invagination of the left auricle in the region of the posteromedial commissure and posterior aspect of the mitral annulus can reduce the herniated leaflet complex, distort the annulus itself and effect better valve closure, thus reducing or correcting incompetence.

Extrinsic Baffle: Various efforts have been made at substituting for the extrinsic baffle effect of the surgeon's extracardiac finger. Ivalon (polyvinyl alcohol)* sponges wrapped on stainless steel wire have been used to maintain this distortion and can indubitably reduce the degree of mitral insufficiency. On the other hand, firmly compressed Gelfoam† can be substituted for the finger and maintain itself even better as a partially absorbable extrinsic baffle. This extrinsic baffle of a firm roll of compressed gelfoam is made to appropriate diameter and length. It is generally 2 to 4 cm in diameter and 8 cm in length. It is held in position without sutures because it rests above the ventricular rim, prevented from downward migration by the left ventricle, prevented from upward migration by the inferior pulmonary vein on the left, the auriculo-pericardial fusion posteriorly, and on the right by the inferior vena cava. Externally it is held in this position by the pericardium. Although the pericardium can loosen and relax the local pressure, it does not do so because of the support from the vertebral bodies.

This simple palliative is appropriate in mild to moderate degrees of mitral incompetence only. It is restricted to valve complexes with minimal calcification. This is a useful "strategic retreat" for the surgeon who anticipates a dominant lesion of mitral stenosis but encounters an unexpected amount of mitral incompetence. It is described at this point because its use involves the reversal of several fundamental hemodynamic and morphologic factors.

METHODS OF SURGICAL TREATMENT

Basically, patients with mitral incompetence fall into four groups.

(1) *Patients With Hemodynamically Insignificant Reflux:* No treatment is in order for the regurgitation *per se*. The correction of coexistent and significant mitral stenosis or myocardial disease requires no elaboration. It is interesting to reflect, however, on the *advantages of bed rest* when the myocardial factor is primarily or secondarily involved in annulus dilatation. From the above described hemodynamic considerations it is apparent that when the stroke volume is reduced at rest, the ventricle is allowed to contract in size, and this may reduce the size of the annulus and the degree of relative incompetence. The same reduction in the size of the ventricle relaxes the taut chordae tendineae and allows better leaflet closure. Thus rest may initiate a *self-correcting* cycle as intricately advantageous as the *self-aggravating* cycle is disadvantageous. If the mitral incompetence is secondary to aortic stenosis with subsequent ventricular failure and dilatation, the aortic stenosis should of course be corrected. Fortunately, the treatment of aortic stenosis has recently undergone improvement.

(*2*) *Patients Who Have Mild to Moderate Insufficiency Associated With Greater or Lesser Degrees of Mitral Stenosis:* This group embraces those patients clinically regarded and operated as having mitral stenosis. This mild or moderate insufficiency is palliated by the extrinsic baffle. The stenosis is of course corrected. We have used this extrinsic baffle more than 200 times. It appears to add nothing to the operative risk of the mitral valve exploration. Patients with only mild to moderate degrees of mitral insufficiency should probably not be offered this palliative as a primary surgical procedure. They will be better advised to be treated medically until such time as their condition worsens or fails to respond to medical maneuvers or until the surgical relief by open or other technics improves.

(*3*) *Patients Who Have Major Mitral Incompetence of Relative or Absolute Nature, or Combinations of the Two:* In this group the leaflets may remain supple, flexible, and useful in the reconstruction of a new valve by valvuloplasty. Here some prefer circumclusion to reduce the valve orifice. This will be further described by Davila, Glover, and their colleagues in this sympo-

* Ivalon Surgical Sponge, Clay-Adams, Inc., New York 10, N. Y.

† Gelfoam Absorbable Gelatin Sponge, the Upjohn Company, Kalamazoo, Michigan.

sium. Our experience with 12 patients has corresponded roughly to the Davila experience with his poor risk group and has therefore been abandoned. Our reasoning was that if the operation were hemodynamically sound, the patient with myocardial as well as valvular disease could tolerate his myocardial disease better without the valvular burden. Inasmuch as these patients were not dramatically relieved, it is presumed that our selection of patients, our technic, the circumclusion technic itself, or some combination of the three were unsatisfactory. We would voice a similar criticism of annulus plication as described by Nichols. No doubt, in their hands as initiating proponents these technics are more satisfactory. We feel that this group of patients will be better handled by a variety of specific internal suture technics possible only through open heart surgery. This approach is principally limited by the hazards of open heart surgery on the left side of the heart *per se*.

(*4*) *Patients With Destroyed or Calcific Valves:* In this fourth group only prosthetic replacement will be effective. Our earlier efforts at the substitution of parts in the form of intrinsic baffles were abandoned because the propagation of thrombotic emboli from the ends of the baffles precluded the use of this procedure in the earlier phases of the life cycle of the disease. If an operation cannot be used because of the inherent dangers in the early phases of a disease, it loses its greatest efficacy. It serves little advantage to correct a valve after irreversible changes have occurred in the heart, lungs, and liver. It is to be hoped that some of the excellent artificial valves now under development will be tolerated without causing embolization. Not until permanent safe effective valve prostheses are available that can be placed with acceptable surgical risk will this great surgical challenge have been met.

Conclusions

The constellation of diseases represented as *mitral regurgitation* requires a variety of surgical corrective technics. Some are available, some are being developed, and the nature of others can perhaps be predicted.

Circumferential Suture of the Mitral Valve for the Correction of Regurgitation*

JULIO C. DAVILA, M.D. *and* ROBERT P. GLOVER, M.D., F.A.C.C.

Philadelphia, Pennsylvania

SINCE the suggestion of annular constriction as a means of correcting mitral regurgitation was advanced in 1954,[1] ample evidence has accumulated which substantiates the soundness of this principle. Whether the best approach to the application of this corrective measure is by closed or open cardiac surgical technic remains to be seen. The mechanical limitations to the use of this approach are determined by those variants of pathologic anatomy of the valve which are present where there is excessive tissue destruction by calcification, distortion, or severe contraction and fixation. Fifty-eight patients have been operated for pure or greatly predominant mitral insufficiency, and substantial to dramatic mechanical correction of the dysfunction was obtained in 55 of them. The effectiveness of this method has been demonstrated on the pulse duplicator even in severely calcified and deformed valves, and in cases of ruptured chordae tendineae.[2,3] Some examples of these demonstrations are shown in Figures 1, 2, and 3.

SURGICAL TECHNIC

The technic used today in this clinic remains essentially unchanged from that which was developed by the authors and reported in previous publications.[4,5] It must be clearly stated at the outset that this procedure is not one which can be applied at once even by the experienced cardiac surgeon. The precise execution of certain maneuvers is essential and requires careful exercise on the living animal heart in the laboratory. Once the spatial anatomic orientation is acquired, however, the technic is quite simple.

Exposure of Heart: A left posterolateral thoractomy incision is used with the patient in the true right lateral decubitus position (Fig. 4a, insert). The 6th rib is resected subperiosteally and the 7th is transected posteriorly removing a centimeter segment and ligating the 6th intercostal neurovascular bundle. Anteriorly the incision is carried slightly beyond the costochondral junction. It is necessary to spread the wound widely using a heavy retractor. The blades should not be posterior to the mid-axillary line in order to avoid hindrance to exposure of the posterior aspect of the heart. The lung is retracted dorsad and somewhat cephalad by the assistant's hand over a moist pack.

The pericardium is incised vertically from the level of the aortic arch passing anterior to the pulmonary hilum and extending down to the diaphragm anterior to reflection of the inferior pulmonary ligament. This incision is then curved ventrad or anteriorly along the pericardiophrenic sulcus to a point a few millimeters behind the phrenic nerve (Fig. 4a). The posterior location of the pericardial incision is necessary to gain access to the posterior surface of the heart without excessive manipulation or dislocation. In advanced cases even slight degrees of rotation of the enormous heart can be catastrophic. After the heart is exposed direct pressure recordings are taken in the left atrium, left ventricle, aorta, and pulmonary artery. Indicator dilution curves with injection of Evans Blue dye (T-1824) in the aorta, left ventricle, and left

* From the Department of Thoracic and Cardiac Surgery and The Thoracic and Cardiovascular Research Laboratory at the Presbyterian Hospital; The Glover Clinic, Philadelphia, Pennsylvania.

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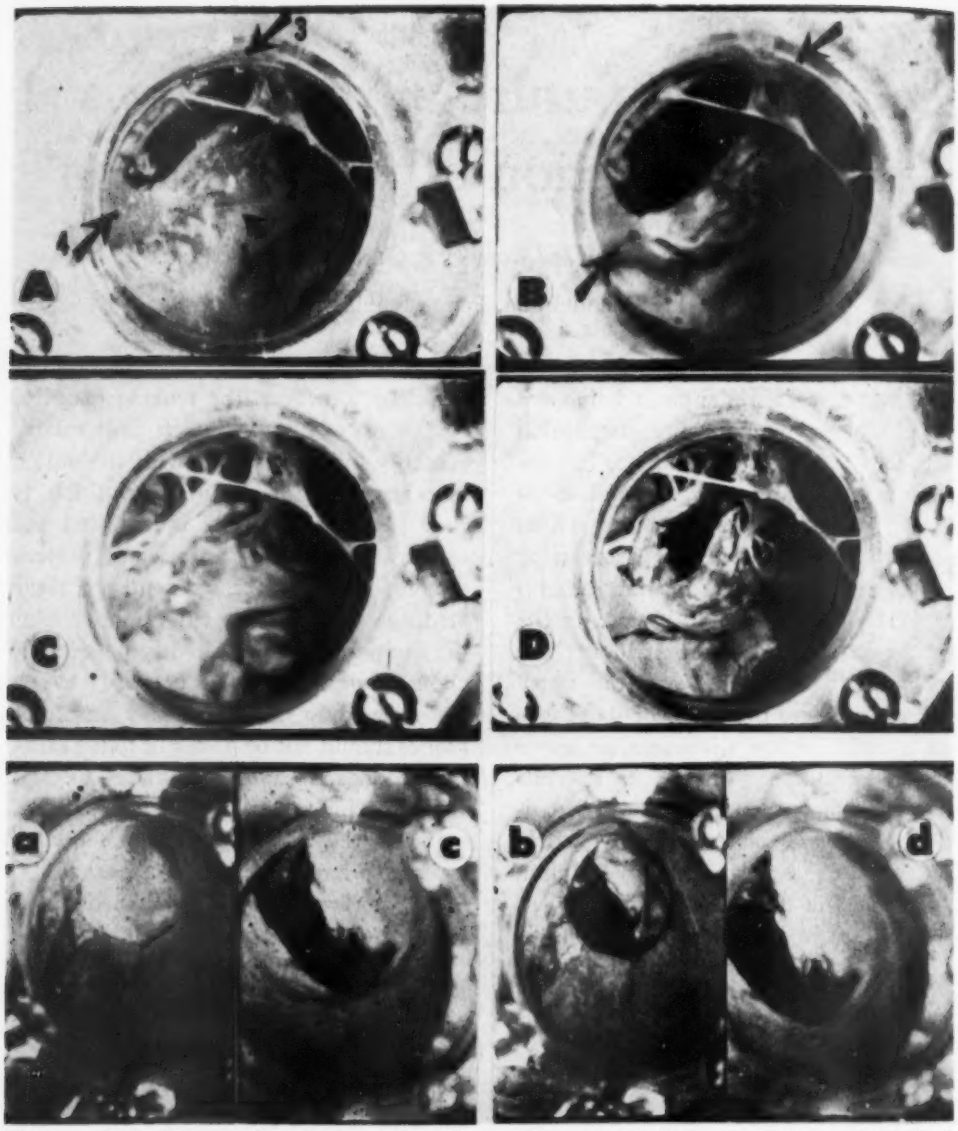

Fig. 1. Single frames taken from moving picture film strips to illustrate various mechanical features of incompetent valves.

From the ventricular side (upper four frames) one can clearly observe the action of the aortic or anterior leaflet of the mitral valve (arrow No. 1) and of its chordae tendineae (arrow No. 2). (A) Systole at maximum approximation of leaflet edges. Arrows 3 and 4 indicate the anterior and posterior commissures, respectively. (B) Shows maximum leaflet retraction in diastole. This is the "effective orifice" of the mitral valve.

Frames C and D show the same valve after correction of regurgitation by circumferential suture. Note complete coaptation in systole (C) and satisfactory retraction in diastole and relaxation of chordae tendineae (D).

Seen from the atrial side (lower four frames), a similar valve is shown to be competent after purse-string suture in frames (a) (systole) and (b) (diastole). Before correction this valve exhibited only slight motion as illustrated in (c) (systole) and (d) (diastole). Note that there is no significant reduction in the size of the effective orifice.

atrium are recorded[6,7] when measurements of cardiac output and central volumes are desired.

A tunnel is then made at the base of the left atrial appendage under the great cardiac vein and the circumflex coronary artery about one

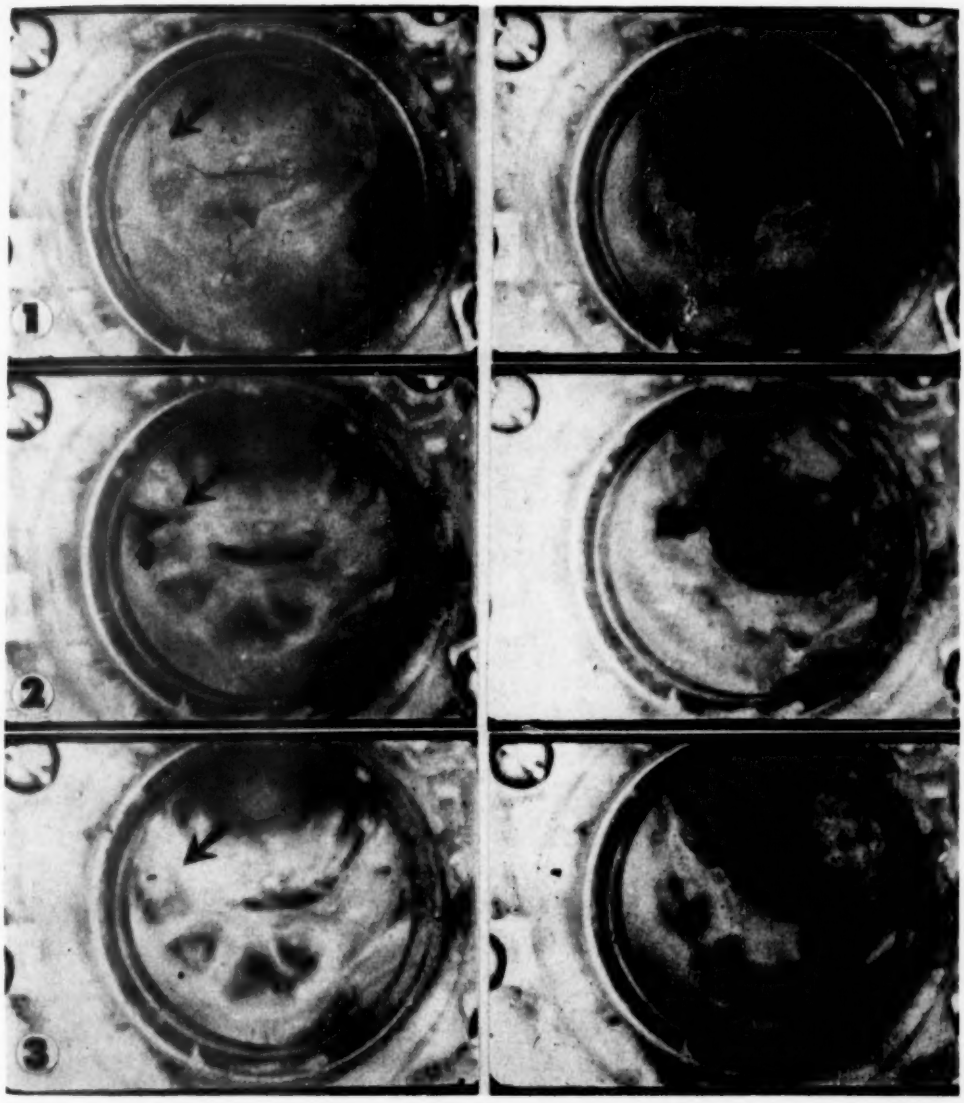

Fig. 2. Following commissurotomy, performed on the pulse duplicator under direct vision, regurgitation was increased due to the laceration of the mural cusp indicated by the small arrow in frame 2. The other arrows indicate the anterior commissure. Regurgitation resulting from inaccurate commissurotomy is satisfactorily corrected by "purse-string" in this specimen. All frames on the left are in systole at maximum closure; on the right they are in diastole at maximum aperture. (1) After anterior and posterior commissurotomy and purse-string. (2) After commissurotomy but before purse-string. (3) The initial state of this valve was one of tight stenosis with slight regurgitation.

centimeter distal to the origin of the anterior descending branch (Fig. 4b).

Examination and Evaluation of Mitral Valve: A hemostatic purse-string of heavy silk is placed around the base of the atrial appendage, a Rummel tourniquet is applied, the appendage is opened, and the left index finger is inserted to examine the valve and evaluate the degree of regurgitation. In typical pure mitral insufficiency the posterior leaflet is often contracted and fused against the myocardial wall. The anterior leaflet usually retains enough area and pliability to be potentially functional (Fig. 1), but is held taut and immobile by the dilated annulus and tense chordae tendineae (Fig. 1, a and b). In valves with combined mitral steno-

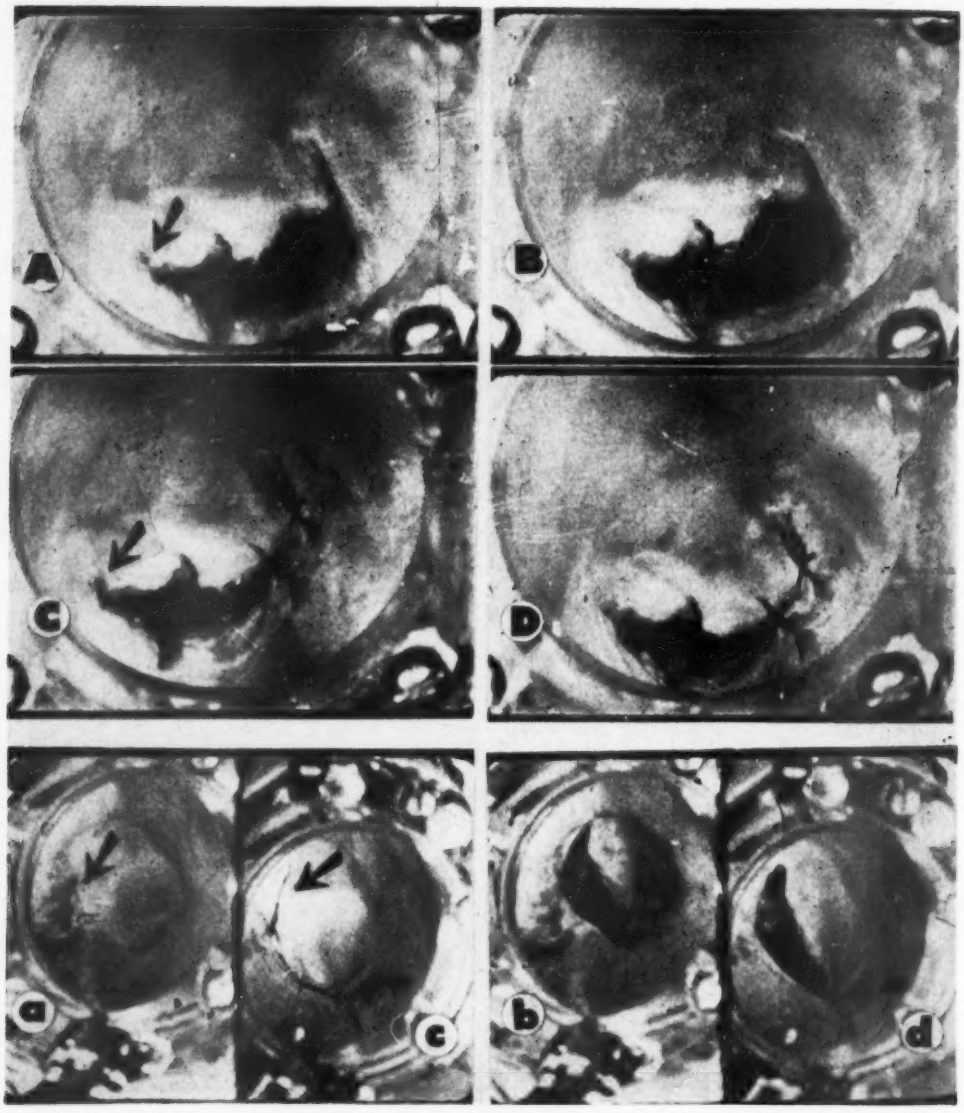

Fig. 3. The comparative efficacy of three different operative technics is illustrated here. These are examples of marked regurgitation in deformed but reasonably pliable valves. The leaflets are tense and move only very slightly in either systole (A) or diastole (B) (upper frames). Suture of the leaflets at the posterior commissure (C and D) reduces the effective orifice but fails to enhance mobility of the leaflet and thus does not improve coaptation (C—systole, D—diastole, upper frames).

In a similar valve the effect of the purse-string operation is seen in (a) systole and in (b) diastole (lower frames). This is compared with the effect of posterior cross plication[8] on the same valve in (c) systole and in (d) diastole (lower frames). Note the laceration about the annulus at the site of suture (indicated by the small arrows). All the large arrows indicate the anterior commissure.

sis and insufficiency varying degrees of calcification and cicatrix may be present (Fig. 2). In the combined lesion where it is necessary to perform commissurotomy in addition to circumferential suture to restore maximum mobility to the valve, the valve is opened after placement, but before tying, of the purse-string suture. As in all pathologic entities for which reparative surgery is attempted, certain lesions will be found which are beyond restoration to satis-

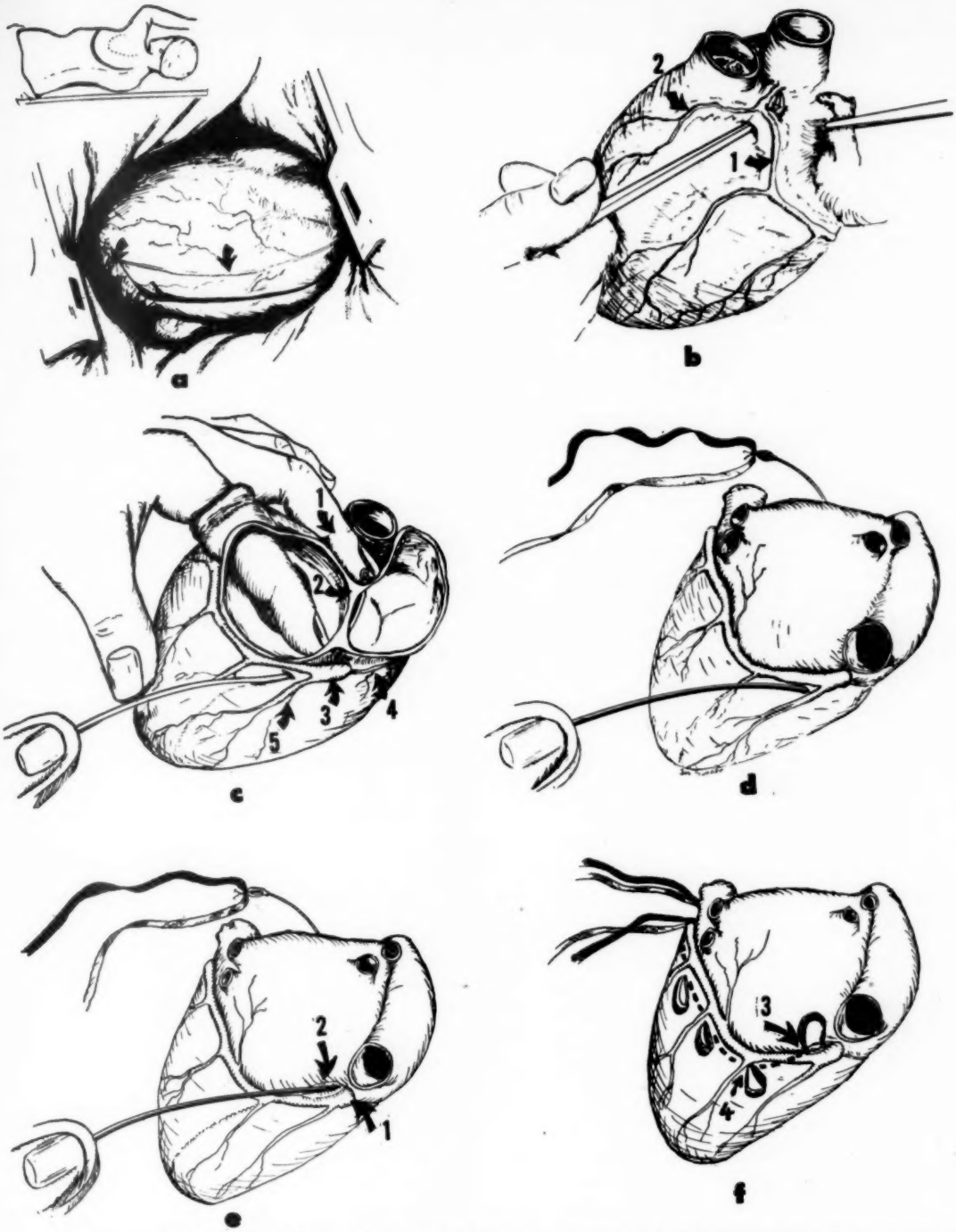

Fig. 4. (a) Insert—the right decubitus position and a left postero-anterior incision are used. It is necessary to expose the heart widely to gain access to its posterior surface. The pericardium is open behind the phrenic nerve (center arrow) from the level of the aortic arch above, to the pericardiophrenic sulcus (arrow, left).

(b) A tunnel is dissected beneath the circumflex coronary artery (1) toward the transverse sinus (see text). (2) The anterior descending coronary artery.

(c) Maneuver of placement of the medial segment of the purse-string. (1) Left middle finger in transverse sinus to receive needle. (2) Pillar forming anterior limit of the interatrial septum and junction of anterior atrial walls. (3) Coronary sinus. (4) Distal segment of right coronary artery. (5) First major vein leading to coronary sinus. This usually marks the course of the posterior descending coronary artery.

(d) The needle in position with wire extended and marked cotton tape attached (see text).

(e) A variation in the maneuver of insertion of the needle. (1) Coronary sinus. (2) Dissection of a groove above the coronary sinus into the A-V groove between this vein and the posterior wall of the atrium.

(f) The posterior tail of the suture is then drawn from the point marked (3) to that marked (4) with a large Reverdin needle. The rest of the encirclement is completed as in Fig. 5.

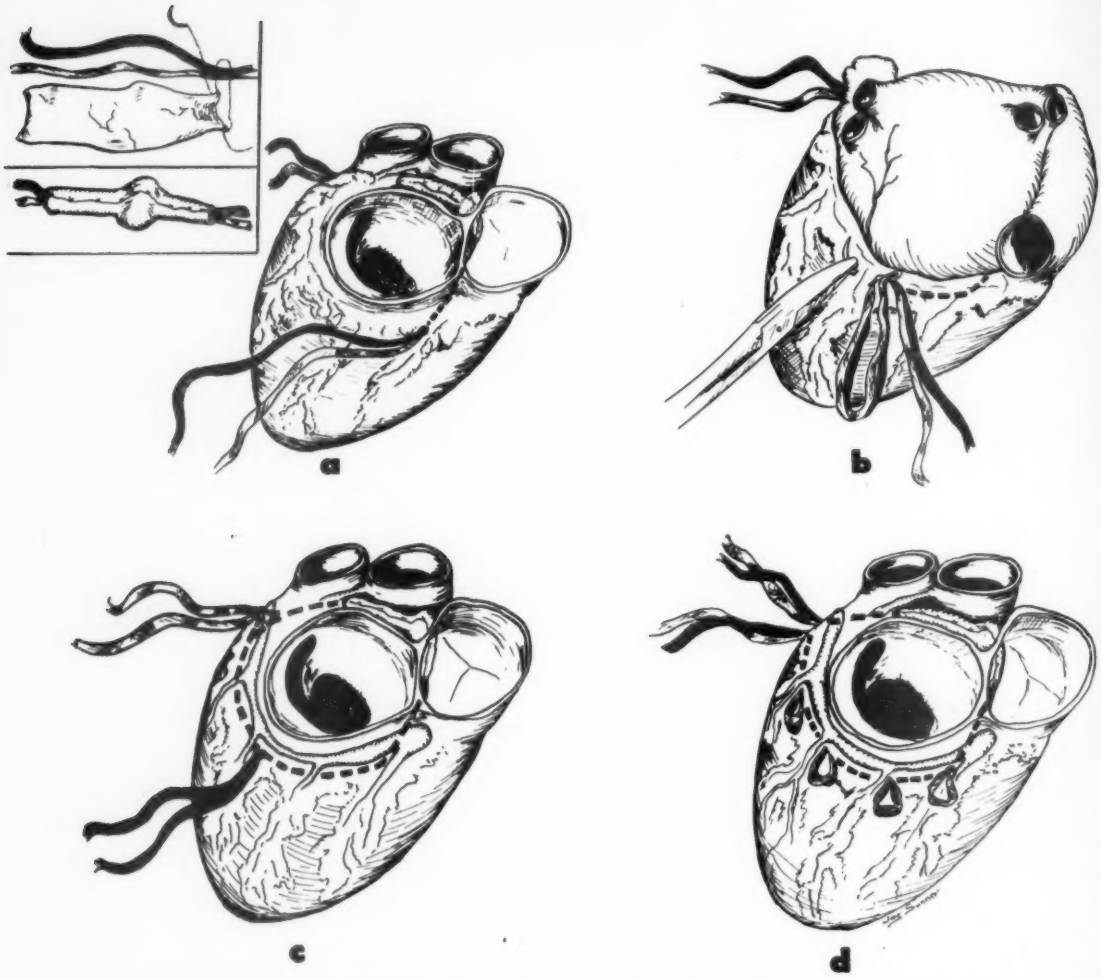

Fig. 5. (a, insert). Construction of the pericardial sleeve with button (see text). The position of the tape and its pericardial cover is shown placed in the transverse sinus, through the tunnel under the circumflex coronary artery anteriorly and through the right atrium and beneath the coronary sinus posteriorly. (b) Placement of the suture in the periannular fat pad (see text). Alternate methods of tying the suture are shown in (c), one segment of the doubled tape is tied anteriorly. The other segment (marked by dyeing half of the tape) is tied laterally. In (d) both doubled tails of the suture are brought out and tied anteriorly.

factory function. It behooves the cardiac surgeon to recognize these prior to inflicting surgical trauma, which, if not satisfactorily corrective, will fruitlessly subject the patient to added risk.

Preparation of Purse String and Pericardial Bolster: After evaluation of the valve, the finger is removed from the atrium and the purse-string with its pericardial bolster is prepared. The suture is made from a doubled strand of one-fourth inch cotton umbilical type of a loose weave* about two feet in length when double. A piece of pericardium 12 cm long and fusiform in contour, being about 3 cm at its center and tapering to $^1/_2$ cm at each end is cut free to make the bolster which will lie in the transverse sinus segment of the annulus. In the experimental laboratory if erosion of the purse-string occurred, it did so routinely in this segment of the ring. This complication was eliminated by the use of the pericardial bolster.[4]

The free piece of pericardium is attached at one end to the center of the cotton tape with fine silk. It is sutured as a sleeve for a length of 2 to 3 cm. A "button" is then made in the bolster

* Gudebrod Bros., Philadelphia, Pennsylvania.

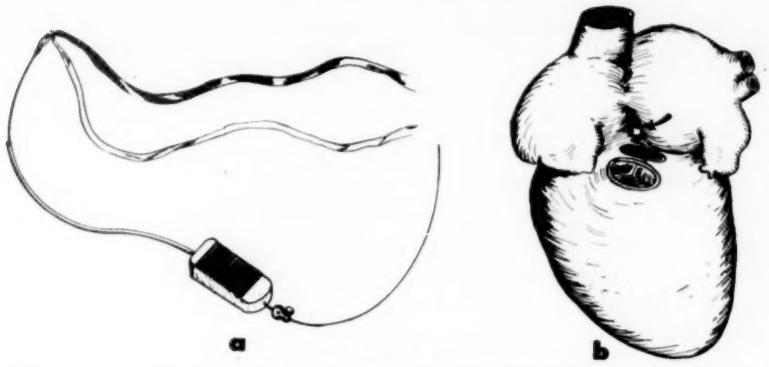

Fig. 6. (a) The special mitral insufficiency needle with extendable eye. (b) This is a sketch of the anterior aspect of the heart with the aorta and pulmonary artery cut away flush with their valve rings. This dissection exposes the anterior surface of the atria and illustrates the dimple (arrow) which forms the anterior base of the interatrial septum. The white dot indicates the site at which the needle emerges from the right atrium.

by "telescoping" a part of it on itself and holding it with sutures to the tape. This "button" will later lie against the point where the suture emerges from the right atrium and will prevent hemorrhage from this site. The remainder of the bolster is completed beyond the "button" as a sleeve. The distal end is not fixed to the tape (Fig. 5a, insert).

The transverse sinus is then explored or dissected carefully to avoid laceration of the atrial walls. The surgeon must be able to palpate the dimple formed at the anterior base of the interatrial septum and behind the aorta (Fig. 6b). This represents the junction of the anterior atrial walls, the interatrial septum, the triangular ligament of the heart, and the mitral, tricuspid and aortic valves and annular framework.

Placement of Medial Segment of Purse-String: For the placement of the medial segment of the purse-string suture a special needle* with its eye on an extendable wire is used (Fig. 6a). The left index finger is inserted through the appendage into the left atrium and is placed on the posterior commissure (Fig. 4c). With two long clamps the posterior edge of the pericardium is grasped and elevated. An assistant gently elevates and very slightly rotates the left ventricle to enable the surgeon to see the posterior aspect of the heart. It is important to keep dislocation of the heart at a minimum throughout this maneuver. In the majority of these cases operated to date, the point of entrance of the needle is just to the left of the posterior descending coronary artery and the first major tributary to the coronary sinus (Fig. 4, c and d). It is important to note that the entrance of the needle is into the fat pad beneath the coronary sinus and distal end of the circumflex coronary artery and *not* into the myocardium itself (Fig. 7).

In the six recent cases of the series a modification in the maneuver of insertion of the needle has been introduced. This was done because in two autopsies it was found that the suture had included one or two large branches of the circumflex coronary artery. In these two instances there was severe adhesive pericarditis and the vessels were difficult to identify. For this reason the initial introduction of the needle was made above the coronary sinus after dissecting into the A-V groove between this vein and the posterior wall of the left atrium (Fig. 4, e and f). After placing the medial zone of the suture, its posterior tail is brought out beneath the A-V vascular bundle using a Reverdin needle. The rest of the encirclement is done as before.

The needle is directed downward tangentially to the annulus and perpendicular to the intracardiac finger which is on the posterior commissure (Fig. 4, c and d). Thus guided, it enters the *right atrium* without entering the left atrial chamber. If the suture should be present in the left atrium, it must be removed and placed correctly.

* George P. Pilling & Sons, Philadelphia, Pennsylvania.

The left middle finger is then placed deep into the transverse sinus into the dimple mentioned above and receives the point of the needle as it is guided along the interatrial septum to emerge from the right atrium. At this point the surgeon can feel a pillar of muscle between the index finger within the chamber and the external finger in the transverse sinus (Fig. 4c). Here again, there is danger of transfixing the left atrium with the needle and caution must be observed to avoid this error. The eye of the needle on the extendable wire is now brought into the field. This feature of the needle enables the suture to be tied to the eye without dislocation of the heart. The double cotton tape is then fastened to the eye with a silk thread so that when it is drawn back the short segment of pericardial sleeve will lie within the right atrium, the "button" will lie snug against the right atrial wall in the transverse sinus, and the major portion of the bolster will lie in the transverse sinus (Fig. 5a).

Placement of Suture in Periannular Fat Pad: After securing the tape to the needle eye, the wire is pulled back and the needle is withdrawn. The posterior tail of the suture emerges from the point where the needle entered. These ends of the purse-string are then threaded through the eye of a broad, flat, slightly blunted fascia needle and the posterior tail of the purse-string is stitched in the fat pad beneath the coronary vessels. It is important in placing this part of the suture that the stitches be made just under the vessels within the fat pad and not into the myocardium. It is also important that each bite begin in the same site from which the previous stitch emerged (Fig. 5, b and d). These fine points in the technic are necessary in order that kinking or damaging of the coronary vessels can be avoided, that further myocardial injury is not done, and so that when the purse-string is pulled down, it can move in the fat pad to closely encircle the annulus (Fig. 7).

Completion of Circumferential Suture: After bringing the posterior tail of the tape around the exterior of the heart to the base of the appendage the pericardium covered portion from the transverse sinus is threaded through the previously made tunnel under the circumflex coronary and great cardiac veins and the two double ends of the purse-string are approximated to complete the circumferential suture (Fig. 5, c and d).

The purse-string is then pulled down by an assistant while the surgeon palpates the disappearing regurgitant jet with his index finger in the atrium. Pressure determinations are made and when the optimum degree of constriction is obtained, the suture is tied in a square knot. Tying of the doubled tails of tape makes a large knot and it occasionally has been found preferable to tie these separately (having previously marked the tape to identify the proper ends) (Fig. 5c). Pressure determinations are again made in the left atrium, left ventricle, aorta, and pulmonary artery and indicator dilution curves are recorded as before. The appendage is ligated and oversewn, the wound is flushed with saline, and the pericardium and chest are closed in the routine manner with a single thoracotomy tube for drainage.

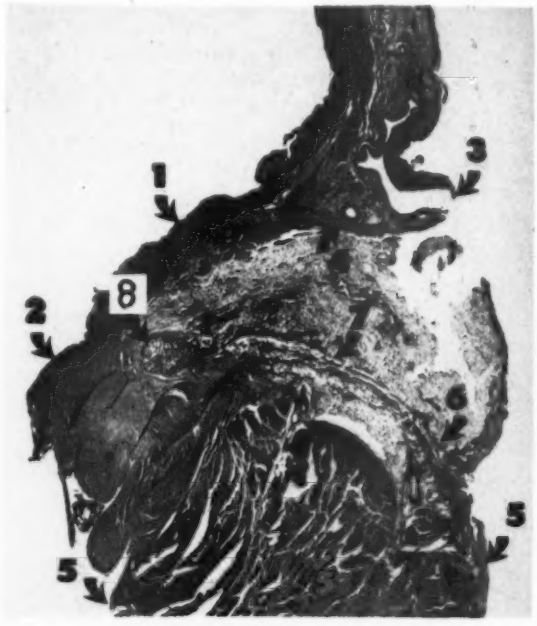

Fig. 7. A section through the lateral zone of the annulus, cutting approximately through the center of the mural cusp. (1) Left atrial wall just above the valve. (2) Base of the mural cusp. (3) Great cardiac vein. (4) Circumflex coronary artery. (5) Ventricular myocardium. (6) Position where suture is placed, superficially in the periannular fat pad. (7) Tract toward the annulus which the suture forms as it is tightened around the annulus. (8) Final position of the suture in the apex of the atrioventricular groove.

Surgical Results

This operation has now been performed in 58 patients. Twenty-five of these patients are considered to have been in medically intractable congestive failure. The operative mortality in this group is 56 per cent. At this writing only three patients of this group are living nine to fifteen months postoperatively; one is slightly improved, one moderately, and the other[3] is markedly improved. Of the others that survived surgery, none has lived longer than ten months postoperatively.

Thirty-three patients have been in stages of severe to moderate failure but all of these have shown some improvement with medical management in the hospital. The operative mortality in this group is 17 per cent. One of the operative deaths was due to an incompatible blood transfusion. Two have died four and eight months following surgery as the result of avoidable technical errors. One died at home one month postoperatively of an acute pulmonary infarct. The 24 remaining patients are alive, 1 to 33 months postoperatively. All of these patients have shown marked, and sometimes dramatic, improvement subjectively and objectively.[3–7]

Mechanically, correction of the regurgitant defect has been attained in 55 cases. In one the mechanical result was undetermined. In two there was total failure to reduce regurgitation because of the nature of the lesion. An excellent degree of correction was obtained in 16 cases, a good correction in 29, and a fair one in 10. This evaluation is based on anatomic changes detected by the surgeon's finger, on hemodynamic observations, and on the x-ray and clinical examinations following surgery.

It is our definite opinion at this time that pure, or massive, predominant mitral regurgitation can be satisfactorily mechanically corrected in a vast majority of patients. In our experience to date, the major problem lies in the selection of patients which hinges on the status of the left ventricular myocardium. It appears that in the cases in which ventricular dilatation has progressed beyond a natural limit recoverability of efficient muscular action is not possible despite adequate correction of valvular mechanics.[7]

Summary

This paper describes in detail the technic for mitral circumferential suture as currently used. It describes some of the minor changes which have been used and emphasizes the reasons for the various steps of the procedure.

The early and late clinical results of application of this operation in 58 patients with severe "pure" or predominant mitral regurgitation are briefly summarized.

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Surgical Treatment of Mitral Insufficiency

Open Approach with Elective Cardiac Arrest*

DONALD B. EFFLER, M.D.

Cleveland, Ohio

INCOMPETENCY of the mitral valve may be congenital or acquired. At present our experience in its surgical treatment is limited—a total of six operations has been performed utilizing a pump-oxygenator. In each operation a transauricular approach has been used while the heart has been arrested with the Melrose technic.[1,2] The results have been gratifying and we are encouraged to broaden our surgical attack upon the incompetent mitral valve.

CONGENITAL MITRAL REGURGITATION

Mitral insufficiency is commonly seen in ostium primum defects of the auricular septum. If such a defect is closed without simultaneous correction of the mitral lesion, the condition will be made worse. The first three patients operated upon in the Cleveland Clinic Hospital for closure of ostium primum defects died within seven to forty days after surgery. Each of these was operated upon with the aid of a pump-oxygenator and elective cardiac arrest, and in each the defect was closed through the right atrium without recognizing the significant mitral regurgitation. Mitral insufficiency usually accompanies an ostium primum defect; the explanation is based on a congenital cleft or failure of fusion of the leaflet in the medial aspect of the valve. The regurgitant stream usually is directed through the large septal defect into the right atrium. After closure of the defect the regurgitation is imposed entirely upon the relatively small left atrium. As soon as the original shunt is no longer a factor, the sudden burden on the atrium proves to be intolerable.

This explanation is supported by our subsequent experience with four cases of ostium primum defect in which the mitral defect was corrected prior to closure of the ostium primum defect; and with one additional case in which a second operation was necessary. After the unfavorable results in the three patients mentioned above, a fourth patient was operated upon for a large ostium primum defect. Again, we did not recognize the significant mitral insufficiency that was present at that time. Although the 14-year-old boy tolerated the initial operation quite well, he developed intractable congestive failure approximately one month after surgery and for the next two months demonstrated slow but progressive deterioration despite bed rest, stringent diet, and intensive medical therapy. In desperation, he was reoperated upon, again utilizing the pump-oxygenator and elective cardiac arrest, and the valve defect was repaired through a left auricular approach. After the second procedure, the patient showed gratifying improvement with reduction in heart size and marked increase in exercise tolerance. Subsequently we had occasion to operate upon four more patients with ostium primum defects, but in each of these we were careful to evaluate the status of the mitral valve and to correct the mitral regurgitation that was present in every case. The results have been far superior in that all of the patients have recovered and appear to have benefited appreciably from their surgical therapy. (Fig. 1.)

Operative Technic: The technical correction of

* From the Department of Thoracic Surgery of The Cleveland Clinic Foundation, and The Frank E. Bunts Educational Institute, Cleveland, Ohio.

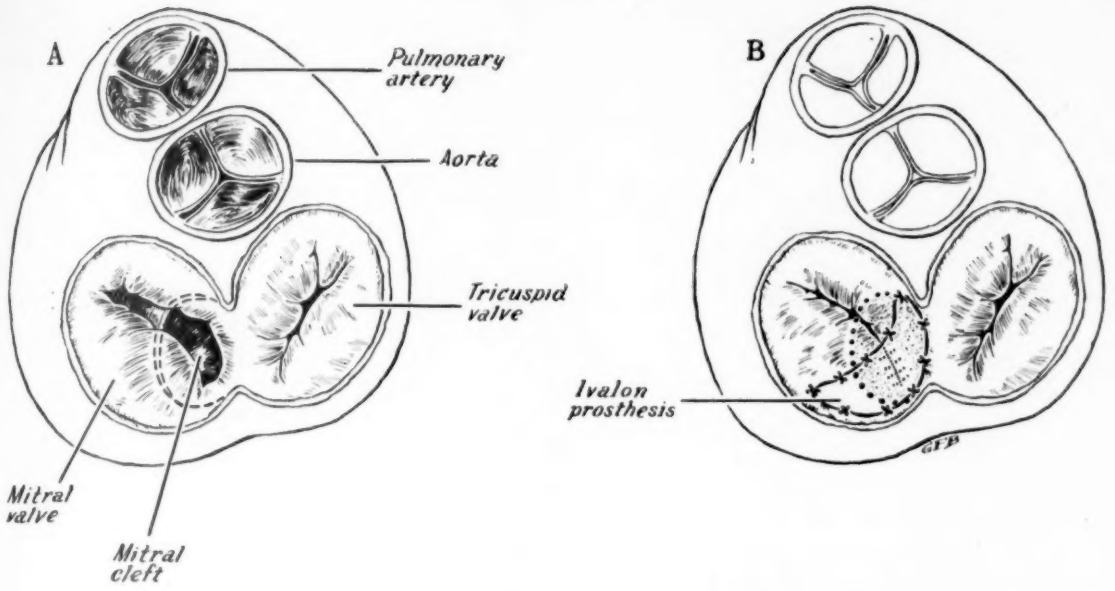

Fig. 1. (A) Schematic drawing of the incompetent mitral valve associated with interatrial septal defect of the ostium primum type. The cleft appears on the medial aspect of the valve and is related to incomplete fusion of the medial commissure. The medial and the eccentric location of the cleft permits regurgitation of the mitral valve into the right atrium. (B) Surgical correction may be accomplished through the large right auricle. Digital palpation via the right auricular appendix will determine the site and the extent of the regurgitant stream—this is performed before the patient is put on the pump-oxygenator run. The technic of correction is similar to that illustrated in Figure 2. The interatrial septal defect is closed by direct suturing after the mitral valvuloplasty is completed.

this one form of mitral insufficiency is relatively simple. Actually, the operation has a double mission: (1) correction of the incompetent valve and, (2) closure of the large atrial defect. This is best accomplished with the arrested heart while the patient's circulation is maintained by a pump-oxygenator. Both objectives may be accomplished through a right auricular approach since there is right atrial dilatation and the septal defect is so large that it permits ready access to the mitral valve. Before starting the pump-oxygenator, the surgeon inserts his index finger through the right atrium and the septal defect, and carefully palpates both the mitral and the tricuspid valve. The regurgitant stream is readily identified and its relationship with the valve cusps is not difficult to ascertain. Usually, the regurgitation is felt on the medial aspect of the valve and is rather sharply localized. When the finger is withdrawn, the patient's circulation is then carried on the pump-oxygenator; the heart is arrested, and the right atrium is opened through a longitudinal incision. The contained blood is removed, and then inspection of the mitral valve under direct vision is easily accomplished. The defect in the valve is not difficult to recognize and its correction may be performed by direct-suture technic with or without a prosthesis. In most cases the cleft is well localized and may be sutured with interrupted silk technic. It has been our practice to place a crescent-shaped prosthesis of pressed Ivalon, or woven Dacron, over the valve repair. The convex surface of the crescent is then sutured to the adjacent annulus; the midportion is sutured to the area of repair itself. The purpose of the prosthesis is to take up the brunt of thrust from the ventricular contraction when the heart is restarted. It has been our fear that the valve, if repaired by suture alone, might fenestrate upon resumption of the ventricular pressures. Following this simple form of correction the septal defect is then closed with interrupted- or continuous-suture technic; again a prosthesis may or may not be necessary, and the operation is then terminated.

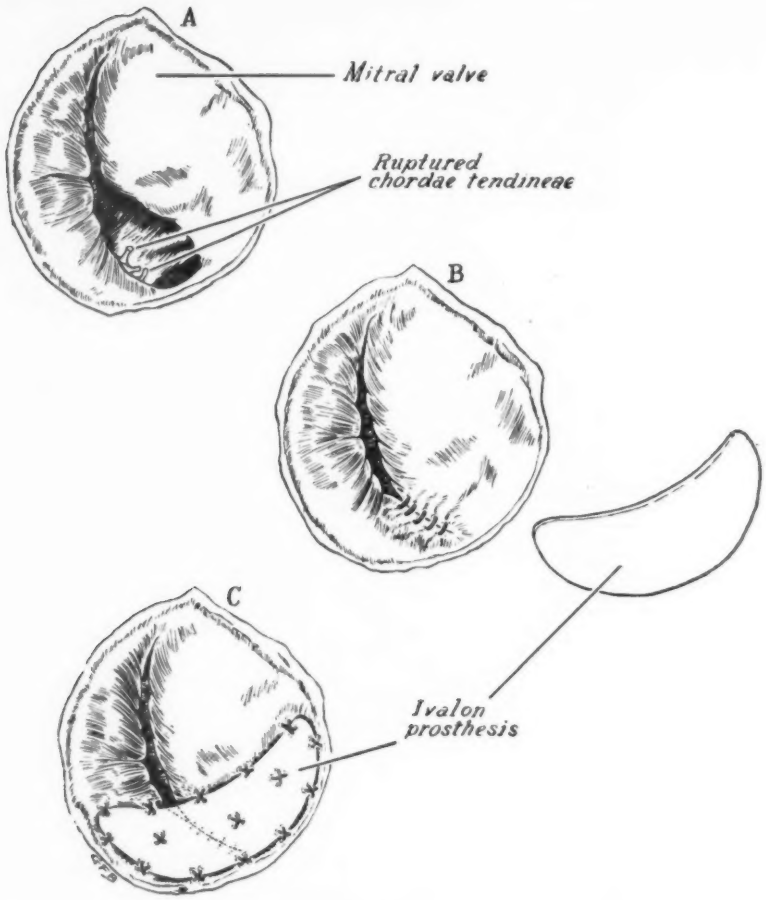

Fig. 2. Surgical correction of mitral insufficiency as performed with the pump-oxygenator and elective cardiac arrest. This method is applicable to those valves with localized regurgitation. (A) Sketch depicts the valve with a localized "flail", secondary to ruptured chordae tendineae. This "tear-drop" effect is seen in old rheumatic fever without flail when the medial portion of the smaller cusp is contracted and fixed. (B) The mitral correction is produced by direct suture to obliterate the involved commissure. Suture closure alone is not enough as the valve may fenestrate by force of left ventricular thrust. (C) Reinforcement of the suture line by the crescent prosthesis. This patch, carefully tailored to the annulus and the involved commissure, distributes the left ventricular thrust over a wide area. In time the patch becomes an integral part of the valve.

ACQUIRED MITRAL REGURGITATION (FIG. 2)

Whereas the lion's share of patients with mitral insufficiency will be classified in the category of acquired disease, our experience in treating the adults with this disease is very limited. As the problems of open-heart surgery with the pump-oxygenator are slowly being resolved we, more and more, have been extending the indications for surgery in adult patients with various forms of acquired valvular disease. At the present time, however, we have operated upon only two adult patients whose primary problems were mitral insufficiency. In two others, we contemplated this direct approach to mitral insufficiency by means of open cardiotomy, but the operation was not accomplished because of fatal technical accidents that are attributable to improper use of the pump-oxygenator and its cannulae. These unfortunate experiences should now be avoidable.

Results: The two patients who were successfully operated upon for correction of their mi-

tral insufficiency have done quite well, and both have shown reduction in heart size and increase in exercise tolerance. Neither patient has been subjected to recatheterization as yet. In both patients the operation was identical: after bilateral anterior thoracotomy had been performed and cannulation was established for the pump-oxygenator, the surgeon's index finger was inserted through the left atrial appendix and the mitral valve was palpated while the heart was actively beating. In both patients the mitral insufficiency was well localized, and in one patient it became obvious that the disease was secondary to ruptured chordae tendineae. As the annulus was dilated in both patients and the valve leaflets were relatively thin, the grave possibility of surgical fenestration of the mitral valve was considered.

The problem was handled in a manner quite similar to that described for the congenital heart lesions. As the disease was primarily confined to the one commissure, in these two patients the posteromedial aspect, the two cusps were approximated at this site by several interrupted sutures to convert, in effect, the mitral insufficiency to a relative mitral stenosis. The valve orifice was closed until it would accommodate two fingers, which was considered an adequate opening for each heart; then the surgical closure was reinforced again by a large crescent- or kidney-shaped prosthesis with its convex side anchored securely to the annulus of the valve. The prosthesis lay firmly over the area of commissure closure after a number of mattress sutures had been used to seat the prosthesis over the valve-suture area. It was our belief that this firm fixation would protect the valve from future fenestration and at that same time divert most of the flow from the midvalve toward the anterolateral aspect. Apparently this has been accomplished to sufficient degree to permit reduction in the size of the heart and marked symptomatic improvement.

Discussion

In the majority of cases a new operation proves to be only another step in the search for the surgical ideal. The procedure that we have employed in seven cases, as described above, has its obvious limitations. Whereas the results are encouraging, it is quite apparent that the technic will be limited in its application. As yet it has not been tried for the most common form of mitral insufficiency—that associated with severe rheumatic valvular cardiac disease.

It is significant, however, that direct inspection of the mitral valve is possible through either right or left atrium when a pump-oxygenator is employed with elective cardiac arrest. The old fear of massive air embolus from the open left side of the heart is no longer a valid one. Since in most patients the left atrium lies posteriorly, it would be thought difficult to visualize its interior even though the heart were bypassed by the use of a pump-oxygenator; however, with the aid of cardiac arrest the heart can be lifted from its bed and rotated or displaced in any manner without the hazard of serious cardiac arrhythmia. The flaccid, arrested heart is indifferent to position or manipulation. This is of extreme importance, as it points to the obvious goal that surgeons will strive for—the replacement of a defective valve by a workable prosthetic valve.

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Addendum

Since the above paper was submitted for publication an additional 12 patients have been operated upon for correction of mitral insufficiency. In each operation total bypass was employed utilizing a disk type pump oxygenator.

With added experience it becomes apparent that the anatomic features of mitral insufficiency may show considerable variation. In the acquired type of mitral regurgitation we have encountered:

(1) The classic "teardrop valve" of rheumatic heart disease.

(2) Ruptured chordae tendineae.

(3) Dilatation of the annulus (etiology uncertain).

(4) Iatrogenic insufficiency following surgical laceration of the mitral valve.

Four of these additional patients did not survive:

one died in the immediate postoperative period, and three of intractable failure within four to five weeks of the operation.

It is now apparent that evaluation of myocardial reserve is of as great importance as the determination of the valvular insufficiency. Even though pressures in the left atrium were reduced by greater than 50 per cent of the preoperative level, the 4 patients who demonstrated cor bovinum relapsed into intractable failure in spite of initial clinical improvement.

Surgical Treatment of Mitral Insufficiency*

Direct Vision Correction with Use of Mechanical Pump Oxygenator and Extracorporeal Perfusion

EARLE B. KAY, M.D., F.A.C.C., CID NOGUEIRA, M.D., JORGE MARTINS DE OLIVEIRA, M.D., *and* HENRY A. ZIMMERMAN, M.D., F.A.C.C.

Cleveland, Ohio

MANY ingenious technics have been devised and enthusiastically advocated in the recent past for the surgical correction of mitral regurgitation. Invariably success was transitory and such operations short lived. The surgeons have been aware in most instances of the inadequacies of such technics and have continuously sought to devise improvements. It has been apparent during this developmental phase of mitral valve surgery that further progress would come only when the mitral valve could be adequately visualized and the various pathologic features appraised, evaluated, and corrected under direct vision. This phase necessitated the successful adaptation of extracorporeal circulation to left heart lesions. Additional knowledge has had to be obtained such as the proper approach and exposure, the advisability of elective cardiac arrest, the prevention of air embolism, and the proper surgical technics. Observations will be presented from experience gained from the direct vision correction of mitral regurgitation in 30 patients.

APPROACH TO THE VALVE

Experience has shown that the mitral valve is best exposed from the right anterolateral approach. This approach not only gives better exposure to all aspects of the operative procedure but also gives greater access to the aortic valve in the event that corrective measures to this valve are found to be necessary; as well as greater access to the heart in the event of ventricular fibrillation or arrest.

ADVISABILITY OF CARDIAC ARREST

The first seven patients to be operated upon had their mitral valvular correction during elective cardiac arrest in the belief that there would be greater safety from the possibility of air embolism. It soon became apparent that to correct mitral insufficiency surgically, the surgeon must have a knowledge not only of the structural changes present but also of the relation between structural changes and functional changes. Functional changes in the case of valvular disease mean motion—the proper opening and closing of the valve. Nothing short of observing the valve mechanism in the beating heart will allow the surgeon information as to the pathologic physiology of that patient's valvular mechanism. The factors contributing to the regurgitation, the site of the regurgitation, and the effectiveness of the correction can all be assessed better with the heart beating.

The greater improvement in the results has borne out these observations so that routinely all patients with mitral regurgitation are now operated upon with the heart beating. There are also additional advantages in maintaining cardiac action in that the myocardium is kept well oxygenated; the operation need not to be hurried; the need to restart the heart is obvi-

* From St. Vincent Charity Hospital, Cleveland, Ohio. Aided in part by a grant from the Cleveland Area Heart Society.

ated; and there have been no associated arrhythmias with such a technic in our series.

AIR EMBOLISM

In this initial series of patients there were four instances of air embolism, one of which was fatal. This entire problem was restudied in the research laboratory with success to the extent that this complication has now been entirely eliminated. A bubble trap was placed in the aortic arch or brachiocephalic artery and pressure recording manometers in the left ventricle and ascending aorta. All of the technical maneuvers incident to mitral valve surgery were then reduplicated. Those maneuvers or situations that could give rise to air embolism were immediately detected and the necessary steps for prevention determined. A left atriotomy could be performed with exposure of the mitral valve without air embolism occurring as long as the mitral valve was maintained in a partially open position so that ventricular systolic pressure would be ineffective and never exceed aortic diastolic pressure. The latter might otherwise occur during the appraisal of the mitral valve following its correction in the presence of a low arterial perfusion pressure or with the use of a highly pulsatile type of pump where ventricular systolic pressure might exceed aortic diastolic pressure.

PREVENTIVE MEASURES DURING SURGERY

During the surgical correction of mitral insufficiency the effectiveness of closure of the mitral valve is so inefficient during the early phases of the procedure that ventricular systolic pressure can never become great and is easily dissipated in a retrograde direction. As the effectiveness of the correction proceeds and as the regurgitation lessens the resistance of the mitral valve to ventricular systole may become sufficiently great as to allow ventricular systole to push air or foam into the aorta. Consequently, as the mitral valve becomes more competent or as the effectiveness of the repair is being evaluated, an area in the valve region that is competent should be kept partially open to prevent the left ventricle from obtaining systolic pressures effective enough to pump air or foam into the systemic circulation. At the completion of the correction, the valve is maintained in this open position until the ventricle and auricle are filled with blood and until the air or foam in the ventricle is either aspirated or pumped back into the auricle.

In contradistinction to those patients having primarily regurgitation, those having a combination of stenosis and regurgitation may have evidence of air at the beginning of the procedure. In instances of stenosis, air and foam may be sucked into the ventricle during diastole while during systole the resistance of the stenosed valve may be greater than the aortic perfusion pressure which may allow this air to be discharged into the systemic circulation.

To minimize this hazard the mitral valve should first be explored digitally. If significant stenosis is present, it should be partially relieved digitally and an instrument inserted to maintain the valve in an open position before the auricle is emptied of its blood content for completion of the commissurotomy and correction of the regurgitation.

PRESENT STATUS OF SURGICAL CORRECTION

Considerable progress has now been accomplished in the surgical treatment of mitral regurgitation. Extracorporeal perfusion technics have been successfully adapted to left-sided cardiotomies allowing the heart to beat so as to properly assess the factors contributing to the regurgitation and to evaluate the effectiveness of the correction without the fear of air embolism or arrhythmias. The majority of the patients with mitral regurgitation can now be benefited greatly by surgical correction and restored to a useful healthful life. In the remaining group of patients not helped or in whom there is a high surgical risk, there are three facets of the problem yet to be corrected or improved. These problems pertain to the patient, the pathology, and the surgical correction.

To be reasonably successful the surgeon must have a patient with sufficient myocardial reserve to withstand the operative procedure, a valvular mechanism that is not so severely destroyed but that it can be surgically corrected, and a surgical technic by which to make this correction. In contrast the surgeon is unlikely to be successful in a patient with severe myocar-

dial failure, a highly destroyed valve, and without a technic for complete valvular replacement for those valves that cannot be benefited materially otherwise. It is not meant to imply that all three of these aspects of the problem go hand in hand, for a patient with a relatively good valve may have a severely dilated and hypertrophied heart. The above problems, however, are responsible for the morbidity and mortality and require further emphasis and improvement.

Myocardial Reserve of Patient: As noted under the section dealing with the selection of patients for surgery, one frequently has little such control over these factors. The incidence of "last resort" surgery is undoubtedly too high. Until recently there was no effective means for surgical correction. Insufficient myocardial reserve to tolerate the operative correction is one of the main causes of failure. The valve may be markedly improved with lowering of the left atrial pressure only to see the heart fail because of its inability to withstand the operative procedure or to pump against the severe pulmonary vascular resistance. This phase, now that there is an effective technic, will with time undoubtedly improve. Patients will be seen earlier while they are in relatively good general condition. Our policy now is that once the diagnosis has been made, and it is evident that the disease is progressive, operative intervention is recommended before obvious myocardial failure or extensive pulmonary vascular sclerosis develops.

Pathologic State of Mitral Valve: The next problem is the pathology. In the future the degree of pathological change will improve with the advent of better management, the use of antibiotics, and earlier surgical intervention. A small percentage, perhaps ten per cent, of valves will still remain which are so severely destroyed that with present technics they still cannot be salvaged. A destroyed valve that cannot be sufficiently corrected to improve the hemodynamics is the other most common cause of failure. To be successful in this group means the solution of the final problem—that of the surgical correction by complete valvular replacement with an artificial valve. Considerable research directed at this aspect is now being conducted at many of the cardiac surgical clinics.

There is no correlation between heart size, myocardial failure, pulmonary vascular sclerosis, and the degree of valvular damage. Patients with a pure mitral insufficiency or in whom the insufficiency is considerably greater than the stenosis frequently have the largest heart, the greatest pressures, and the most severe degree of myocardial failure, but yet have a valve in which the cusps and musculotendinous mechanism are not severely destroyed but quite pliable and surgically workable. Such valves lend themselves ideally to surgical correction so that the hemodynamics are immediately improved with striking reduction in left ventricular strain and rapid convalescence, even in the presence of little myocardial reserve. On the other hand, another patient with a smaller heart might have a valve so severely destroyed by calcification, loss of valvular tissue, or destruction of the valvular musculotendinous mechanism that surgical correction is practically impossible. The stenosis can be relieved as far as digital pressure is concerned and the regurgitation corrected, but yet valve function—the opening-closing mechanism cannot be properly restored. To suitably benefit such a patient would require complete valve replacement.

Selection of Patients

In the recent past, prior to an effective technic for the surgical correction of mitral regurgitation, considerable effort was exerted in the selection of patients for valvular surgery, directed at excluding patients with mitral regurgitation or multivalvular disease. Many diagnostic tests were employed to aid in this differentiation, including left-sided cardiac catheterization, Evans blue dye dilution curve, and diodrast studies. Although these examinations in skilled hands are not associated with any great degree of complications, they are still formidable and frequently exhausting to the sick cardiac patient, in addition to which they frequently do not provide the desired information. Since we now have effective surgical technics to cope with regurgitant lesions in the majority of instances, as well as multivalvular disease, the need for the more precise preoperative information is less important in view of the fact that such can be readily obtained at the time of

surgical exploration by pressure studies and direct examination.

Preoperature Evaluation: The history, clinical course, and physical examination still remain a very important aspect of the appraisal. The electrocardiogram and roentgen examinations give valuable information as to chamber hypertrophy and dilatation. It is particularly valuable to have the previous studies available for comparison to determine whether significant change or progression of the disease has occurred. Phonocardiograms are employed for comparison with postoperative studies. A definite improvement in the valve sounds is now being seen, which was a very infrequent occurrence in patients operated on with closed technics. Right-sided cardiac catheterization, with and without exercise, a simple and entirely safe technic, is routinely employed to determine the status of and changes in the pulmonary vasculature, as well as providing information regarding cardiac output and reserve. Pulmonary wedge pressure studies obtained at this time not only provide an index as to left atrial pressures but also provide suggestive evidence as to the presence of regurgitation or stenosis, or both.

It is important to determine the presence or absence of rheumatic activity by sedimentation rates, the presence of C-reactive proteins, and a period of observation in the hospital of temperature and pulse. Liver and kidney function tests are employed when indicated. In some instances a longer period of observation is necessary to determine the patient's response to definitive therapy in the presence of failure.

Criteria for Recommending Surgery: If the above studies show the patient to be symptomatic, to have an enlarged heart, electrocardiographic evidence of left atrial and ventricular overloading, evidence of pulmonary hypertension aggravated by exercise and without signs of activity, operation is recommended. This is particularly so if serial examinations reveal a definite progression in such signs, especially with regard to the x-rays and electrocardiogram. An increase in the size of the cardiac silhouette, as well as a progressive shift of the mean electrical axis to the right, expression of a more and more aggravated pulmonary hypertension, constitute important evidence. The cardiopulmonary reserve is frequently relatively good in patients with mitral regurgitation. Once there is evidence of progression of the above signs, however, we believe it is unwise to postpone operation to await more urgent indications because of the detrimental effect on the myocardium, which may compromise an otherwise successful result.

Surgical Technic

Pump Oxygenator: All of the patients have been operated with the use of the Kay-Cross rotating disc oxygenator. Because of the extraordinary amount of blood that may be regurgitated into the auricle, even in the presence of a normal aortic valve, it is necessary to have adequate sump facility to handle as much as two to three liters of blood if necessary. We have employed two sumps—one with a filter system—to be used in the event of considerable calcium deposits or clot, and the other without. Two bubble traps are available to handle this increased sump load, if necessary.

A flow rate usually of 50 cc/kg/min which results in an arterial inflow of 3 to 3.5 *l*/min has sufficed to maintain a mean arterial pressure of 70 to 80 mm Hg. The inflow cannula is always in the common femoral artery through the superficial femoral artery. The venous return to the oxygenator has been by sump suction regulating the venous return by maintaining the vena caval pressure at pre-perfusion levels. This, we feel, gives us a better control over body blood balance. Constant monitoring of the mean arterial pressure, mean vena caval pressure, electrocardiogram, electroencephalogram, pO_2, pCO_2, and pH, body and oxygen temperature, provide us with a constant physiologic status of the patient. Hematocrit, hemoglobin, and body weight are determined immediately prior to and following surgery. The patient is placed on a heated mattress with the right side elevated between 20 and 30 degrees.

As an anterolateral incision with transection of the sternum is being made, the femoral cannulations for arterial input, arterial manometer, and intravenous infusion are being simultaneously completed.

Exploration and Visualization of Valve: A

routine re-evaluation of the heart is first made. The status of the tricuspid valve is determined by digital exploration. Pressure recordings of the aorta and left ventricle are then obtained to verify or eliminate co-existent aortic valvular disease. Pressure recordings of the pulmonary artery and left auricle are then made. The extracorporeal perfusion is then begun while the left auricle is incised and the mitral valve digitally explored. If the mitral valve is obviously incompetent, the sump then empties the left auricle of its blood content so the various factors contributing to the regurgitation can be further visualized and assessed. If a significant degree of stenosis is also present, the valve is opened as widely as possible digitally and an instrument is inserted between the valve leaflets prior to aspirating the blood from the auricle. The commissurotomy is then completed under direct vision. This is followed by mobilization of the valve cusps and chordae tendinae.

Repair of Valve: In patients with pure mitral insufficiency, it has been necessary not only to plicate the annulus at both the commissures but also anteriorly and posteriorly. As the valve becomes more competent, it is important to keep an area of the valve separated to allow regurgitation as other aspects of the valve are being evaluated. Several mattress sutures should be used in each area so that an adequate apposition of tissue is forthcoming and the sutures are without tension.

In patients with mixed mitral stenosis and regurgitation, it is important that a complete commissurotomy and valve leaflet mobilization be accomplished prior to correction of the insufficiency for otherwise an extensively calcified commissure prevents or may prevent annular approximation by plication. If a highly calcified commissure or cusp prevents cuspal approximation, this calcium can be largely or partially removed and the residual opening can be obliterated by incorporating a plug of Ivalon in the plication. In an occasional patient one of the mitral cusps—usually the mural—will be so destroyed from the rheumatic involvement as to lack adequate valvular substance. In such instances valve substitution in the form of compressed Ivalon (10 to 2) can be incorporated on the ventricular aspect of the cusp. In two patients, the regurgitation present resulted from an inadvertent cut into the leaflets adjacent to the lateral commissure by a commissurotomy knife during a previous operation at another hospital. Such tears are first repaired by mattress sutures, followed by a commissurotomy and annular plication.

Results of Surgery

Factors Influencing Results: The incompetent valves in the majority of patients with mitral regurgitation can be surgically corrected by the technics described. The ease and effectiveness of the correction is largely dependent upon the severity of the pathologic process. Valves composed of severely matted cusps and chordae tendinae, those showing loss of valve substance, or those which are highly calcified, are the most difficult to repair. Short of complete valve replacement, the surgeon in some instances must be content with a result short of ideal, obtaining as much improvement as possible by the plastic procedure and the addition of the plastic prostheses that are available at the present time. The role of chronic myocarditis, myocardial failure, pulmonary vascular sclerosis, and the presence of other valvular defects also are important factors in the eventual result. Fortunately, the pathologic process in the majority of valves is such that they can be corrected and the myocardial reserve is usually sufficiently great as to provide satisfactory function. With continued progress in this field, earlier surgical intervention, and probable lessened severity of the pathologic process from improved therapeutics, greater benefit can be anticipated in the future.

It is too soon to attempt an evaluation of the surgical results obtained in patients with mitral regurgitation corrected by the open technic, for this group has only been operated upon within the past year. However, comparison to the early results obtained previously by closed methods allows for considerable enthusiasm for the open technic at present. The eventual results will be dependent not only upon the effectiveness and permanence of surgical repair, but also upon the myocardial reserve and the reversibility of pulmonary vascular changes.

Objective Evidence of Improvement: Left atrial

pressures were recorded pre- and post-correction in ten instances. Prior to surgical correction there was an average left atrial pressure of 40/22 mm Hg, as contrasted to only 16/5 mm Hg following the relief of the regurgitation. The marked improvement in the atrial pressures obtained immediately postoperatively, the rapidity of convalescence, the decrease in heart size, and the rapid increase in exercise or work tolerance in the majority of patients following operation all point to a gratifying eventual result. Routine cardiac evaluation studies, including cardiac catheterization, are obtained six months to one year following surgery. Time has not allowed the complete performance of these studies as yet.

Operative Mortality: There were seven deaths in this group of 30 patients for an operative mortality of 23 per cent. An analysis of the cause of death in these patients shows that in the future with greater experience some of these deaths can undoubtedly be avoided. Failure, in three patients, was thought to be due to the presence of a severely destroyed valve in which sufficient surgical correction could not be obtained. Two patients died immediately postoperatively from what was felt to be poor myocardial reserve with myocardial failure. One patient died from either air or calcium embolism. The remaining death was from an electrolyte imbalance and renal failure. The patient had a longer perfusion period than usual due to the inability to maintain a satisfactory cardiac output. An atrial septal defect was later found that had not been detected previously. As soon as this was closed the heart was then able to maintain a good output.

In the future it is felt that complications due to air embolism can be prevented and those due to electrolyte imbalance largely overcome. Three of the initial seven patients operated upon with cardiac arrest have only had fair results while all the remaining patients operated upon with the heart beating have had excellent results.

Summary

We have described our experiences during the past year with the direct vision surgical correction of mitral regurgitation in 30 patients operated on by the extracorporeal circulation technic with the heart beating.

It is felt that with the use of a mechanical pump oxygenator, direct vision correction of mitral regurgitation will now be a realization in the majority of such patients. The valves in a few patients are so destroyed that nothing short of valve replacement will suffice. The operative mortality and morbidity during the developmental phase has been low. Some of the technical factors contributing to this mortality and morbidity are correctable. Others, such as extensively destroyed valves, pulmonary vascular changes, and poor myocardial reserve, may be largely avoided by earlier surgical intervention.

Reports on Cardiac Surgery

Hypothermia for Open Heart Surgery*

F. John Lewis, M.D.

Chicago, Illinois

A number of striking changes, most of which signify a reduced metabolic rate, accompany a carefully controlled lowering of the body temperature. The oxygen consumption falls rapidly as the temperature is lowered and while the oxygen needs of the tissues are reduced during moderate hypothermia the blood flow to the entire body or to any region of the body may be occluded for a much longer time than is tolerated at normal body temperature. Thus time is provided to do some types of surgery in an open, dry field while the blood flow is interrupted—an advantage which has proved to be particularly useful in cardiac surgery.

The technic I have used for open heart surgery during hypothermia may be illustrated by describing the operation to repair atrial septal defects, since our greatest experience with hypothermia has been in the repair of these defects. We have successfully employed hypothermia to do this operation for approximately five years.

Technic

Under deep anesthesia with thiopental sodium and gallamine triethiodide (Flaxedil®), sufficient to suppress all shivering, the body temperature is lowered by surface cooling to about 29° C (84.5° F) (Fig. 1). An automatic respirator which administers 5 per cent carbon dioxide in oxygen by a semiopen system is used from the beginning of cooling until late during the rewarming period. This respiratory technic is employed to avoid dangerous shifts in blood pH which occur with manually assisted respiration which is invariably irregular. The use of 5 per cent carbon dioxide prevents the respiratory alkalosis which would otherwise occur at the low body temperatures when an effective respirator, such as ours, is used.

An anterior transverse incision which opens both pleural spaces is used. After the heart has been exposed, it is explored by inserting a finger into the right atrium through the auricular appendage in order to identify the anatomy of the defect and to detect, if possible, any associated anomalies. By learning as much as possible about the defect before the circulation is occluded, the operator can avoid confusion and save time later while the heart is open.

After the preparations are completed for the open cardiotomy, the total cardiac inflow is occluded by tightening tapes around the superior and inferior venae cavae and the outflow is occluded by clamping the aorta and the pulmonary artery with one large clamp. The right atrium is then opened widely to expose the septal defect in a blood-free field. A running suture, reinforced with additional interrupted stitches, is sufficient to repair the defect. After the left and right atria have been filled with saline or blood, the cardiotomy incision is closed with a clamp and circulation is restarted. The atrial incision is then repaired over the clamp. The total occlusion time has averaged four to five minutes though eight to ten minutes would doubtless be safe in most of these patients at the body temperature we employ. As soon as the chest wound has been repaired we immerse the patient in a bath of hot water at 112° F and keep him there until his

* From the Department of Surgery, Northwestern University Medical School.

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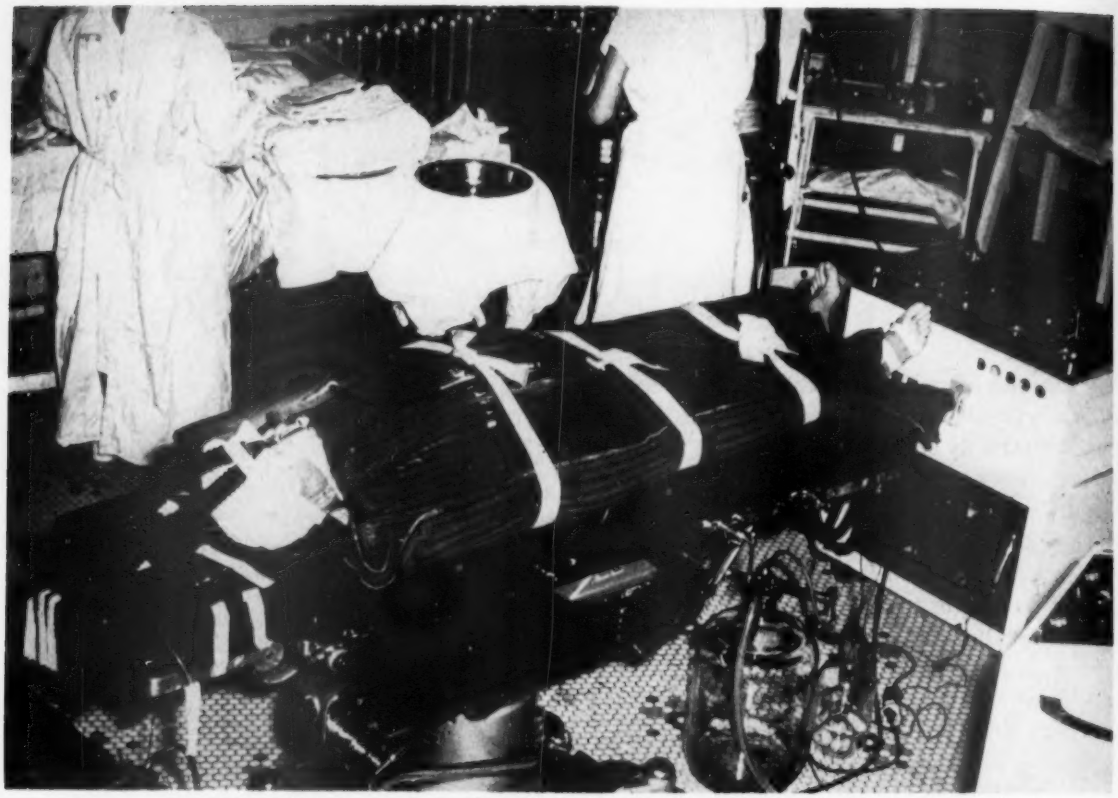

Fig. 1. The patient is being cooled with refrigerating blankets while he is deeply anesthetized.

body temperature reaches 93 to 95° F (Fig. 2).

Once the temperature has reached normal the postoperative course of these patients is similar to that of other patients undergoing cardiac surgery. Adult patients may lose as much as 1,000 cc of blood through the chest catheters during the first 12 postoperative hours, but I am not certain, from my own experience, that they bleed more than individuals subjected to operations of similar magnitude at normal body temperature. In any case, the major blood loss is promptly replaced, and in addition, blood is given if there is any apparently unexplained drop in blood pressure during the early postoperative hours. We have not encountered any vague "rewarming shock" in these patients.

Clinical Applications

ATRIAL SEPTIC DEFECTS

The technic of hypothermia for open heart operations seems to be particularly suitable for this defect and the results following repair have usually been good. The method has been used to operate upon 65 patients with atrial septal defects. There were seven operative deaths in the series though there has been only one death among the last 21 patients. Thus the present risk of the operation among the patients for whom we have advised surgery would appear to be well below 10 per cent and probably about 5 per cent.

Age has not proved to be a contraindication to use of this technic nor has size. Though children withstand hypothermia much better than adults, adults tolerate the procedure quite well. Most of the patients have, in fact, been adults. The median age was 23 with an age range of 3 to 61 years. Ten of the group were over 40 years of age. The largest patient weighed 199 pounds. The oldest patient and the largest patient both survived with good clinical results.

Subjective and objective clinical improvement has been the usual result among the patients who have been followed for six months or more

Fig. 2. The patient is being rewarmed in a tank of hot water after completion of the operation. The arterial manometer, automatic respirator, and oscilloscope are shown above the head of the tank while the rectal thermometer is shown at the foot of the tank.

postoperatively. Of the three clinical failures among these patients two were patients who had persistent ostium primum defects and complete heart block following the operation. The third clinical failure was in a patient with severe mitral insufficiency. The objective evidence provided by postoperative cardiac catheterization also demonstrated the success of the operation. Among 30 patients undergoing postoperative catheterization, evidence of a remaining shunt was found in only two.

Hypothermia is an effective technic for repairing the majority of atrial septal defects. The persistent ostium primum defect has been troublesome but the repair of this type of defect is likely to be hazardous by any method. The results have been gratifying among patients with foramen ovale defects, and in most cases of the high atrial septal defect.[3]

The usual type of atrial septal defect (foramen ovale defect) is probably the simplest intracardiac defect for which an open operation is indicated. Since hypothermia has been successful in repairing this type of defect it is logical to ask whether or not the method should be extended to other types of open intracardiac surgery. There is not general agreement on this point, nor, for that matter, is there general agreement that hypothermia should be used to repair even atrial septal defects. It does seem, however, especially to those who have had some experience with the technic, that hypothermia is an effective way of operating not only on atrial septal defects, but on some other cardiac anomalies as well.

PULMONARY STENOSIS

Swan and his associates have been the principle advocates of the open operation using hypothermia for isolated pulmonary stenosis.[2] Their experience now extends to 38 operations and their results have been excellent. The mortality rate has been low and they have achieved an impressive reduction in the pressure gradient across the pulmonary valve—to normal in most cases. This appears to be a better achievement than is obtained with a blind transventricular operation, and though I may lack sufficient personal experience with this operation, I feel that this technic is the best, at present, for congenital isolated pulmonary stenosis.

AORTIC STENOSIS

With a similar, though more difficult and complex technic, the aortic valve may also be exposed for an open operation. We developed a technic for operating on this valve directly during hypothermia[4] and found later that Swan had developed a similar technic and preceded us in its clinical employment.[7]

This operation involves an approach to the aortic valve through the ascending aorta after the cardiac inflow has been interrupted and the ascending aorta has been occluded distal to the site of the aortic incision. Special precautions are taken to avoid left-sided air embolism.

This open operation should prove to be better

than the various blind transventricular or transaortic approaches to the aortic valve. With the blind operations it is unlikely that more than one commissure of the fused valve is opened but it is quite possible to inadvertently tear into one of the cusps and thus produce an aortic insufficiency. With the open operation, on the other hand, the surgeon can accurately open the three commissures out to the aortic wall. When the valve is heavily calcified and stiff even this open operation may not change the functional dynamics of the valve greatly but it should lead to some improvement in the function of most stenotic valves and great improvement in few. A simple opening of the commissures under direct vision may be all that we can hope to accomplish surgically in this disease until it finally becomes possible to replace the deformed valve with a satisfactory new one. To date we have used the open operation for aortic stenosis in four patients with one death.

VENTRICULAR SEPTAL DEFECTS

After working for some time with experimental ventricular septal defects, I felt that hypothermia would prove to be a satisfactory method for the repair of the clinical defects, but extracorporeal pump-oxygenators came rapidly into the field, after a slow start, and they have now been used more for the repair of this particular defect than for any other. It is quite possible that hypothermia will never receive more than the sporadic testing it has already had for the repair of these defects. These defects are more difficult to repair than atrial septal defects and hence more operating time is greatly to be desired. Furthermore, a ventriculotomy seems to be particularly hazardous under hypothermia due to the high incidence of ventricular fibrillation. A ventriculotomy may not, however, be necessary for repair of the usual ventricular septal defect because most of the membraneous defects can be exposed very well through the right atrium. If they were to be repaired under hypothermia this would be the sensible approach. This may also prove to be the best approach for repairing the defect by any technic if there is an associated pulmonary hypertension. The right ventricle would then be better able to bear its heavy postoperative load.

OTHER LESIONS

We have used hypothermia successfully for two relatively uncommon lesions: one a case of total anomalous pulmonary venous drainage in which all the pulmonary veins entered the right atrium, and the other a case of tri-atrial heart. The preoperative diagnosis was correct in the first case but the second case was encountered unexpectedly while operating for what was presumed to be an atrial septal defect. In neither instance was more than seven minutes required to make the repair. Myxomas of the heart which project into the right atrium may also be a suitable, though relatively uncommon, lesion for open surgery under hypothermia.[1]

Discussion

The field of intracardiac surgery is in turmoil. There is disagreement concerning the place of closed technics, concerning the safety and effectiveness of various types of pump-oxygenators, and in some cases, concerning the critical question of whether or not surgery is actually indicated for some of the cases subjected to surgery at the present time. In this active field it is difficult to define the place that hypothermia should occupy at the present time, and it would be rash to guess what its future will be. The defects that have been repaired with impressive success employing hypothermia (atrial septal defects and isolated pulmonary stenosis) are still being repaired with closed technics by a number of surgeons, while others are beginning to use pump-oxygenators for these same lesions. There is not yet enough evidence at hand to allow a clear-cut decision in favor of one technic and it is quite possible, of course, that such evidence will not soon be forthcoming. More than one technic may find a place for the repair of some intracardiac anomalies. As in the past with other surgical technics, surgeons keenly interested and experienced in a particular special technic, such as hypothermia, may employ it effectively while others accomplish as much with other special technics.

Hypothermia appeared on the scene as a sort of short cut for operating within the open heart while extracorporeal pump-oxygenators, after many years of investigation, were still apparently too unwieldy and unpredictable. Now these

machines have at last blossomed forth and it might be expected that hypothermia would soon fade away, but there are still some difficulties with the pump-oxygenators. The most popular type of oxygenator, the bubble-oxygenator, is even now, at least in the experimental laboratory, occasionally dangerous and unpredictable. While these machines are in a relatively primitive stage of development hypothermia may still be useful, for it has some attractive features. It allows open repair of some intracardiac defects in a bloodless field, without complex equipment, without a special team of assistants, without special blood donors, and without heparinization of the patient. Adults offer no special problems. Its chief disadvantage is the limited time period provided for the intracardiac procedure. This time period may be extended by adding coronary perfusion[6] or by using lower body temperatures,[5] but we have not felt that either of these additions or, for that matter, extracorporeal pump-oxygenators, were needed in order to close the repairable atrial septal defects, correct isolated pulmonary stenosis, and perhaps correct some cases of aortic stenosis under direct vision.

Summary

(1) For open intracardiac operations to repair atrial septal defects under hypothermia the patient's body temperature has been lowered by surface cooling to approximately 29° C (84.5° F). Sixty-five patients with atrial septal defects have been operated upon by the technic described and five minutes of cardiac inflow occlusion has been sufficient to repair most of the defects.

(2) Hypothermia also provides an effective method for operating on a few other intracardiac defects such as isolated pulmonary stenosis and aortic stenosis under direct vision.

(3) Some of the advantages and disadvantages of hypothermia are discussed.

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Remedial Lesions of the Mitral and Aortic Valves*

ELMER R. MAURER, M.D., F.A.C.C. *and* F. L. MENDEZ, JR., M.D.

Cincinnati, Ohio

DESPITE the amazing and very rapid development, during the past few years, of closed as well as open surgical technic for the correction of congenital and acquired lesions of the heart, stenotic and regurgitant lesions of the aortic valve and regurgitant lesions of the mitral valve still present problems in complete cure which remain unsolved. Suggested surgical approaches for these lesions are numerous, but few of these operations can be routinely employed as practical methods of treatment. Periodic re-evaluation of surgical operations for any disorder in any part of the body is always desirable if one wishes to obtain the best results with the least amount of risk. With this thought in mind, we have reviewed our own personal experiences with disorders of the mitral and aortic valves and present our impressions about what constitute, at least at the present time, working practical operations which can and should be suggested in the management of mitral and aortic stenosis and insufficiency.

MITRAL STENOSIS

At the present time there is little if any disagreement among cardiovascular surgeons that mitral commissurotomy is the procedure of choice in the management of so-called purely stenotic lesions of the mitral valve. Whether the valve should be approached from the right or the left side of the heart by closed technics, or by open cardiotomy, is being tested at the present time. In either event commissurotomy, as we know the procedure today, gives very excellent results in 85 to 90 per cent of the cases of mitral stenosis, providing the patients do not have irreversible myocardial damage or pulmonary arterial hypertensive changes. It is noteworthy that in the course of development of the operation, mitral commissurotomy, the attempts of the original investigators were directed at relieving the associated pulmonary hypertension. These operations included such procedures as the removal of the cardiac accelerator fibers to produce slowing of the heart rate and increased ventricular output, destruction of the tricuspid valve producing an insufficiency in this structure to lower the pulmonary arterial output, production of communicating shunts between the pulmonary and systemic venous systems by anastomosing the azygos vein with the dorsal division vein of the lower lobe to reduce the hypertension in the left auricle, and the production of an interauricular septal defect to relieve pulmonary hypertension. These procedures, in light of our very effective modern direct approach to the stenosed mitral valve, seem illogical and radical. However, we recount them to point up the fact that operative procedures popular today may next year be considered outmoded or without good basis.

We feel that mitral commissurotomy as it is practiced at the present time is without doubt the best surgical approach to the stenosed mitral orifice. In the past it has been suggested that the commissures should be completely opened and that an orifice of at least two fingers or 4.0 cm^2 should be obtained if one wishes to have a good result. In our own practice we very definitely make a particular attempt to open both commissures completely, but regardless of the size of the heart, we feel that an adequate

* From the Department of Surgery, University of Cincinnati, College of Medicine.

opening is obtained if following commissurotomy the index finger can be kept in the mitral orifice during all phases of the cardiac cycle without cardiac standstill.

Mitral Insufficiency

During the past nine years investigators who previously considered mitral insufficiency to be a relatively benign lesion now look upon this disorder as a very much more severe clinical entity than mitral stenosis. Much knowledge of the disease of insufficiency has been obtained from findings made by the numerous digital examinations during the intracardiac surgical treatment of mitral stenosis. It has become obvious, with the passage of time, that in some 15 per cent of the cases of mitral stenosis it is absolutely impossible to determine accurately prior to operation whether stenosis is the predominant lesion. In such instances mitral valves have been explored under the impression that stenosis was the predominant lesion, only to find at the time of operation that almost a pure state of mitral insufficiency existed.

Development of the surgical approaches to mitral insufficiency in the past have been along the lines of direct suturing of the insufficient valve leaflets or the introduction of plastic and pericardial devices into the left ventricular cavity to occlude the insufficient valvular opening. These methods in clinical application soon proved impractical because of incomplete correction of the insufficiency and the generally poor clinical results. In 1954 Davila, Glover, and co-workers,[1] after a concentrated study of the pathophysiologic derangement of the mitral valve and annulus, made the very important observation that mitral insufficiency is the result of three basic pathologic changes, viz., absolute loss of valve tissue, contraction and foreshortening of the chordae tendineae and dilatation of the mitral annulus or ring. For surgical correction of mitral insufficiency to be effective, one must consider each of these factors which may be operating independently or together.

*Technic of Mitral Purse-string:** We have followed the technic of mitral purse-string as outlined by Glover and Davila.[2] The index finger of the left hand is inserted through the purse-stringed left auricular appendage and by palpation of the interauricular septum is used as an indirect guide for the passage of the Davila needle (Fig. 1) into the chamber of the right auricle beginning at a point to the left of the posterior descending coronary artery. Using the left middle finger as a guide in the transverse sinus the point of the needle is guided out through the right auricular wall at the base of the interauricular septum. The wire in the central portion of the needle is then advanced so that a double small sized umbilical tape can be threaded. The needle is then passed in reverse manner through the right auricle bringing the purse-string suture out of the posterior aspect of the heart. Anteriorly the purse-string is passed under a previously developed tunnel beneath the circumflex coronary artery just beyond its origin from the septal branch. The posterior end of the purse-string is passed by

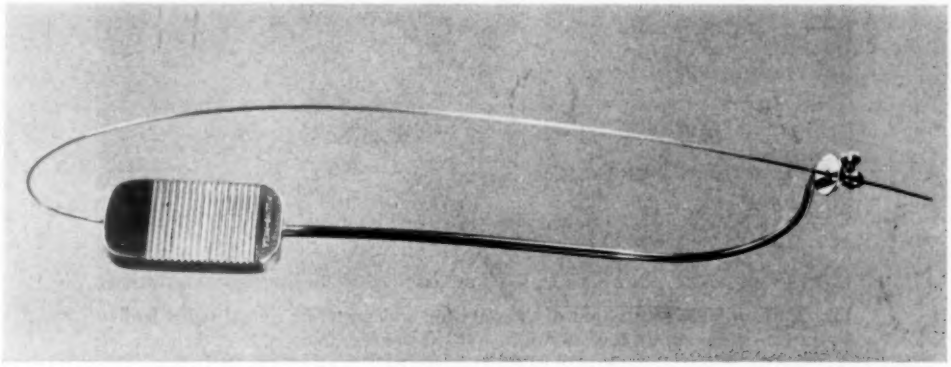

Fig. 1. Davila needle especially designed for easier placement of the mitral purse-string.

* Described in detail p. 267.

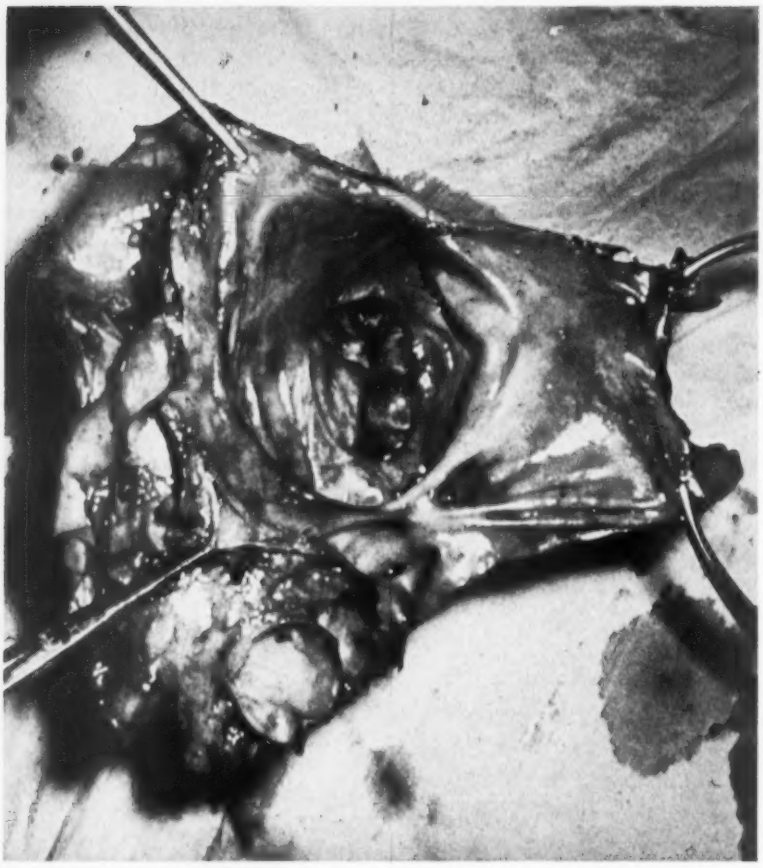

Fig. 2. Complete coaptation of the anterior and posterior mitral valve leaflets by purse-string about the annulus. Valve viewed from above through left auricle.

needle suture technic beneath the descending branches of the coronary artery over the ventricular wall. The purse-string suture is then tied in place by an assistant while the operator evaluates the complete correction of regurgitation with the intra-atrial finger. In all patients the regurgitation was completely corrected. It is an impressive experience to see an unusually large, tense left auricular chamber suddenly lose its high pressure and decrease rapidly and dramatically in size, following application of the purse-string suture.

Intracardiac pressure records are obtained in the left ventricle, left atrium, pulmonary artery, and aorta both before and following completion of the mitral purse-string operation. Such pressure tracings are a more direct indication of degree of correction of the insufficiency by the operative procedure. The advantages of the mitral purse-string operation are that the majority if not all of the mitral insufficiency is corrected and it does not produce mitral stenosis. The procedure results in no injury to the myocardium, coronary arteries, or the conduction system.

We have had occasion to study a purse-string in an individual who was considered for salvage surgery and who subsequently died six months after a mitral purse-string procedure because of a large dilated insufficient left ventricle. As can be seen in the photograph of the specimen, the mitral annulus reduced in size so that there was good coaptation of the valve leaflets (Fig. 2). There was no cutting through or erosion of the wall of the left auricle (Fig. 3). The exposed portion of the tape in the interior of the right auricle was covered with endothelium. This patient obviously had complete correction

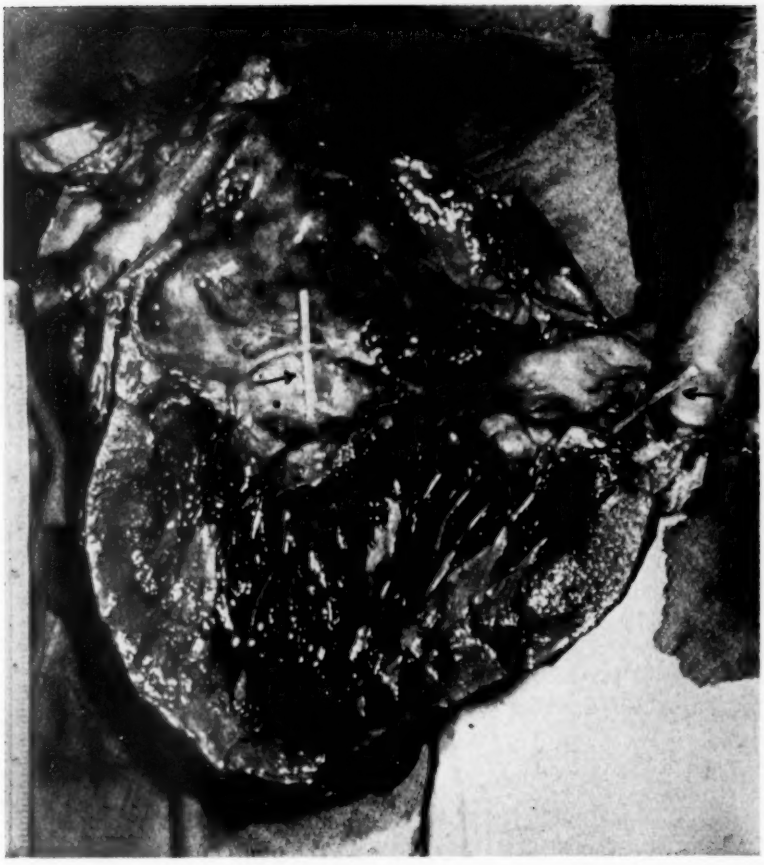

Fig. 3. Open heart specimen demonstrates no erosion of the left auricle or annulus. Arrows indicate course of purse-string. Left ventricle is markedly dilated.

of the valvular defect, but died as a result of left ventricular insufficiency which had become irreversible. Such a finding would suggest that best results will be obtained if operation is performed while dilatation of the ventricle is reversible. In summary, we believe that the mitral purse-string operation at the present moment offers the best method of complete cure of mitral insufficiency with the lowest morbidity and mortality rate.

Open Heart Technics: A few patients have been operated upon by open technics utilizing heart-lung machines in several clinics over the country in an attempt to correct mitral insufficiency by direct suture of the valve leaflets. If, however, the leaflets are diseased or far apart, coaptation is extremely difficult by simple suture technic. Suturing the annulus is also necessary, particularly where the ring is dilated, to protect the leaflet suture line. It is our feeling, therefore, that very probably open direct approaches to the problem of mitral insufficiency will eventually be the procedures of choice, but that the mitral purse-string will still be of real help in those instances where it is necessary to reduce the size of the mitral annulus. In other words, a combination of open as well as circumferential surgical technics may be necessary to control all aspects of the problem of mitral insufficiency.

Aortic Stenosis

Aortic stenosis is now regarded as one of the most serious of all of the valvular diseases. It is most commonly an acquired condition resulting from rheumatic fever, arteriosclerosis, bacterial endocarditis, or syphilis. The lesion may also be congenital in origin. It may or may not be

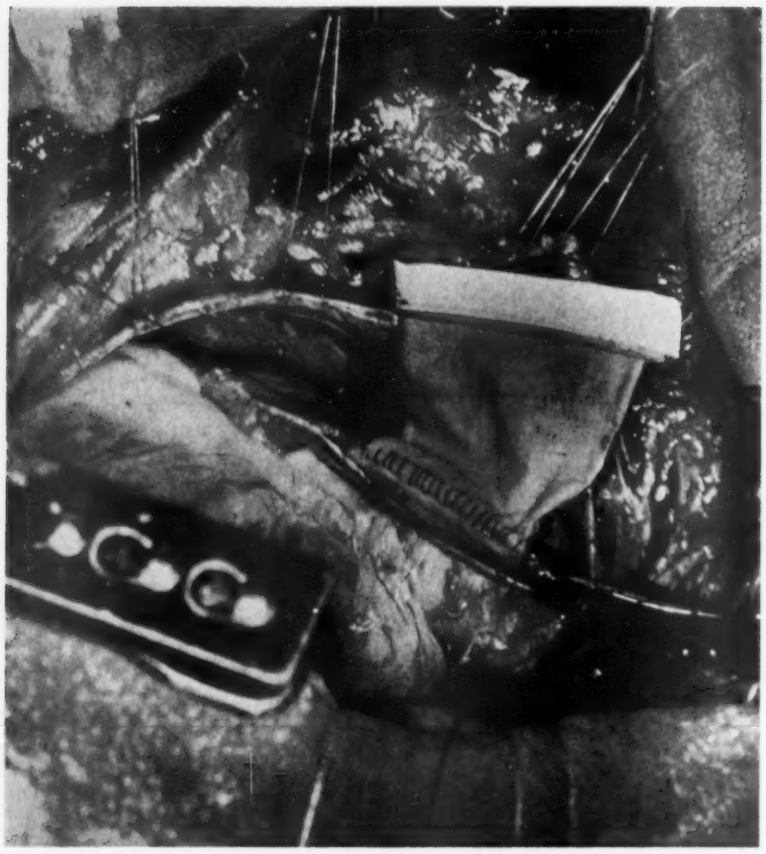

Fig. 4. Photograph of Swann tunnel sutured to incision in exteriorized "lip" of ascending aorta.

associated with aortic insufficiency, and quite commonly occurs as an independent disorder.

Surgical attempts at correction of aortic stenosis probably began as early as 1947 with the work of Horace G. Smithy[3] of South Carolina. Smithy in his experimental work passed a specially devised valvulotome in retrograde fashion by way of the ascending aorta through the stenosed aortic valve. In 1950 Bailey and his group[4] also reported on their transaortic approaches to the aortic valve. Both groups of investigators finally concluded that perhaps the transventricular route would be preferable because of the inaccessibility of the aortic valve when approached with instruments through the aorta and difficulties experienced in controlling hemorrhage by the aortic route. In 1952 Bailey and his associates[5,6] developed the triradiate dilator which was passed by way of the ventricular chamber through a small incision controlled by a purse-string suture in the wall of the left ventricle. The results from this approach, however, also proved to be extremely unsatisfactory with high mortality rates varying from 24 to 25%. Hemorrhage presented as an uncontrollable feature of this operation because of the soft, sometimes cheesy, consistency of the ventricular myocardium, making suture closure of the incision impossible. Also surgical approaches through the left ventricle often resulted in ventricular fibrillation which was irreversible and resulted in death.

Transaortic Technics: At the International Symposium on Cardiovascular Surgery at Henry Ford Hospital[7] in Detroit, Michigan in March, 1955, the whole problem of surgical approach to stenotic lesions of the aortic valve was reviewed and it was the consensus at that time that the transaortic operation was now certainly the most desirable one because of the

Fig. 5. Photograph of index finger inserted by way of tunnel through ascending aorta into aortic valve.

good results and lower mortality rate. In 1953 Bailey and his associates[8] suggested the use of a tunnel-graft of pericardium attached to a small incision in an exteriorized lip in the wall of the ascending aorta as a channel of approach to the aortic valve. We personally have preferred the transaortic approach utilizing the tunnel developed by Wm. K. Swann and his associates of Knoxville, Tennessee.[9] In this procedure the aortic valve is approached through a longitudinal sternal splitting incision. A small lip of the ascending aorta just distal to the aortic valve is then exteriorized with a vascular clamp. Incision is made in the exteriorized portion of the aorta and the Swann tunnel is sutured in place (Fig. 4). As the clamp is released the index finger is passed retrograde by way of the tunnel down to the aortic valve (Fig. 5). Utilizing either finger fracture technic or commissurotomy knives the commissures are divided out to the annulus. A small purse-string suture keeps the Swann tunnel snug about the index finger during the intra-aortic manipulation.

The results obtained by transaortic commissurotomy will depend in great part upon the etiology of the lesion producing the stenosis. With aortic stenosis resulting from rheumatic fever one could anticipate commissural fusion characteristic of this disease and a good result therefore should be expected. The arteriosclerotic form of aortic stenosis, on the other hand, is characterized by marked hardening of the valve leaflets due to the deposition of calcium salts. Characteristically, there is no commissural fusion and in such cases commissurotomy would give a poor result.

Open Heart Technic: Congenital aortic valvular stenosis is characterized by a megaphone-like structure and in our opinion should be best

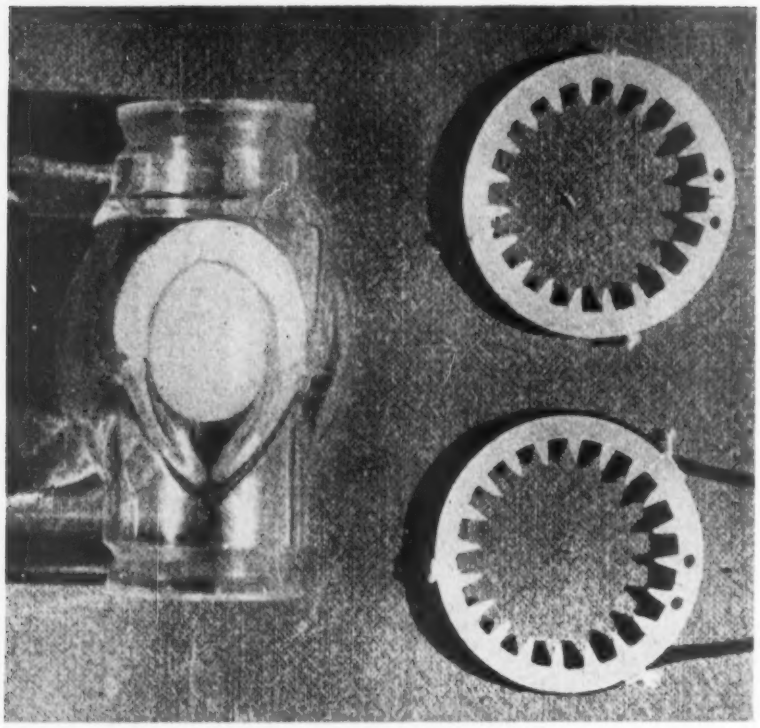

Fig. 6. Hufnagel valve and nylon rings for securing the valve in the descending aorta.

approached by open arteriorrhaphy using the extracorporeal heart-lung machine. Extracorporeal circulation with elective cardiac asystole or coronary sinus perfusion would be necessary because of the hazard of air embolus during the open operation exposing the coronary ostia. Surgical treatment regardless of method of approach is hopeless when calcifications are so extensive as to form a solid block involving all of the valve tissues. Good results cannot be anticipated in this type of disorder regardless of whether the closed or the open method of approach is used.

The mortality rate in recent reports of open approaches to aortic stenosis has been extremely high. Enthusiasm originally expressed for this new approach is beginning to decrease and it is our personal opinion that at the present time closed transaortic commissurotomy is the procedure of choice in aortic stenosis due to rheumatic fever.

Coronary insufficiency with pain is not only not a contraindication to surgery, but on the contrary would suggest that the operation was extremely urgent.

Aortic Insufficiency

Wide open aortic insufficiency is usually an acquired lesion resulting from rheumatic fever, bacterial endocarditis, syphilis, or trauma. It is rarely congenital. Insufficiency also is very rarely associated with stenosis of the aortic or the mitral valves.

Individuals with wide open aortic insufficiency are not unlike patients with aortic stenosis in that they are also liable to sudden death, emphasizing the common factor of relationship between coronary flow and cardiac work.

Surgical approaches to the correction of the problem of aortic insufficiency have essentially been along two lines, namely circumferential purse-string about the base of the aortic valve and the Hufnagel plastic valve inserted into the aorta. Circumferential purse-string at the base of the aortic valve has not received widespread acceptance because of the problems involved in

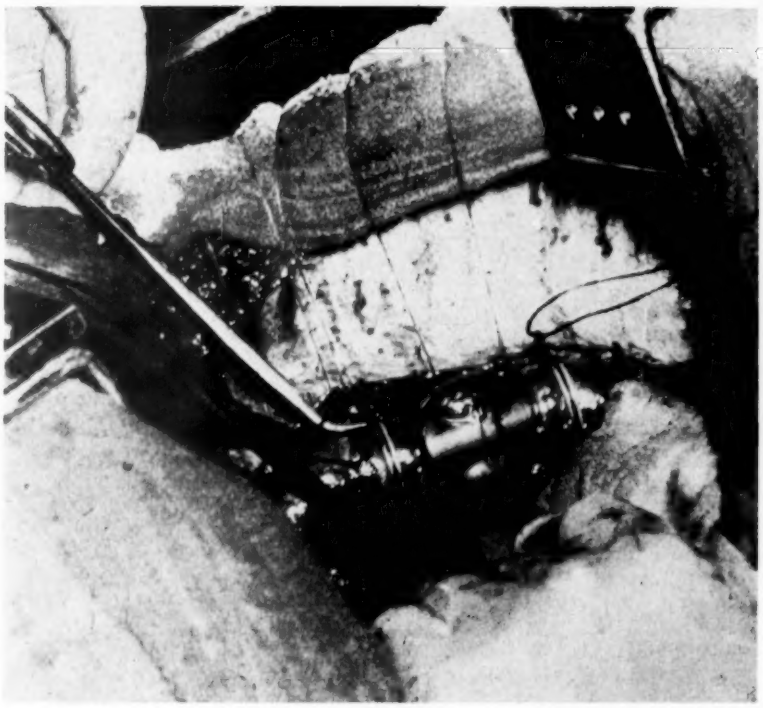

Fig. 7. Photograph of Hufnagel valve secured in descending aorta just beyond origin of left subclavian artery.

seating the purse-string below the valve cusps. In other words, there is a constant tendency for the purse-string to ride up with consequent occlusion of the coronary orifices. On the other hand, the Hufnagel valve at the present time appears to offer the only real solution, although incomplete, to controlling this highly fatal abnormality.

Hufnagel Procedure: Hufnagel began his work in 1948 using homologous transplantations of human valve tissue. The initial response to this transplant was usually excellent, but long term results with these transplants, as well as valves made from arterial or vein tissue, were not too good because of the effect of wear and tear over a period of time. After extensive experimental investigation, Hufnagel[10,11] developed an ingenious procedure which involved the insertion into the aorta of a plastic valve made in a single piece out of methyl methacrylate and polyethylene (Fig. 6). In the construction of the valve, flow factors were calculated so that the available surface inside of the valve was approximately two times the area of inlet. To fix the valve in the aorta it was necessary to devise a method of circumferential securing so that necrosis of the vessel wall did not occur. Accordingly, the multiple point fixation ring made of nylon was developed. The ring teeth were slightly longer than the thickness of the aortic wall and so spaced as to allow nutrient vessels to pass through to the cuff beyond the point of circumferential fixation (Fig. 6). The site for insertion was chosen at a point just beyond the left subclavian artery (Fig. 7). Experimental work has definitely indicated that it would not be advisable to insert the valve in the ascending aorta between the orifices of the coronary arteries and the vessels of the head because of the possible reduction of backflow during diastole and the correspondingly reduced flow through the coronary arteries.

The patient with aortic regurgitation undoubtedly has an undesirable balance between the augmented work load due to regurgitation and the limited oxygen available to the myo-

cardium due to the low coronary perfusion pressure during ventricular diastole. In other words, the patient has relative coronary insufficiency.

Following placement of the Hufnagel valve there is undoubtedly a reduction in the volume of regurgitation which is another way of saying there is a reduction in the ventricular work load. It has been estimated that 60 to 75 per cent of the effective cardiac output passes beyond the mouth of the left subclavian artery and through the plastic valve into the distal aorta (Fig. 7). In other words, approximately 60 to 75 per cent of the ventricular overwork is removed. To this factor is attributed the real benefit of the operation. At the same time, unfortunately, the coronary artery perfusion pressure is uniformly decreased usually by 50 per cent. It is obvious therefore, that improvement in any individual patient will depend in great part upon the preponderance of reduction of work load of the ventricle and minimal reduction in the coronary perfusion flow.

Intravascular hemolysis with consequent anemia very commonly occurs following the insertion of the lucite ball prosthesis into the aorta. This is due to gradual destruction of the red cells by the action of the lucite ball. The lowest hematocrit reading can be anticipated on or about the sixth to eighth postoperative day.

It has been definitely demonstrated that one response to anemia is a decrease in the coronary vascular resistance. Patients with aortic regurgitation already have a relative coronary insufficiency and, therefore, mild degrees of anemia will have a very adverse effect upon the coronary circulation and myocardial function. Actually when coronary insufficiency is present, degrees of anemia which are normally well tolerated will substantially depress the ventricular function. It is important, therefore, that these individuals be followed carefully by multiple hematocrit readings and receive transfusions regularly until stabilized. Usually 24 days after the onset of red cell destruction, the erythropoietic activity has already set in and the hematocrit has begun to return to preoperative levels.

Obviously it is important that the fixation rings be properly placed so that there will be no slippage of the aorta. Air embolism is prevented by aspirating all existing air from the valve with a needle inserted through the aortic wall and filling the valve with saline solution.

Peripheral embolization presented as a problem in approximately 15 per cent of the original series of Hufnagel. This complication due to the development of a thrombus ring about the area where the cuff overlaps the valve has been completely corrected by wrapping the area with a piece of elastic Orlon cloth. It is important that the valve is seated into the aorta in such a manner that it is not angulated.

Experimental work involving plastic operations by open technics on the aortic valve up to now have not been encouraging. At the present time the Hufnagel operation appears to offer the best prospects for relief of anginal pain and dyspnea and should be suggested as the method of treatment in selected cases.

Summary and Conclusions

(1) A current review and evaluation of working practical operations for the correction of mitral and aortic stenosis and insufficiency has been presented.

(2) Critical preoperative evaluation of the pathological characteristics of the valve lesion aids appreciably in the selection and application of the proper corrective operation.

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Autogenous Lung Oxygenation during Cardiac Bypass*

Experimental Studies and Clinical Application in Aortic Valve Surgery

GUMERSINDO BLANCO, M.D., CLEMENTE OCA, M.D., SALVADOR LAGUNA, M.D., LUIS E. NUNEZ, M.D., JACK SCHAEFER, M.D., *and* CHARLES P. BAILEY, M.D., F.A.C.C.

Philadelphia, Pennsylvania

A NUMBER of technics are being employed at present to sustain the vital processes of circulation and oxygenation of the blood during "open" cardiac surgery. The vast majority of these methods employ a mechanical pump-oxygenator and the variations in apparatus and in the principles involved in their operation are legion. Without doubt, we shall soon witness a process of selection and simplification whereby many of these technics will be discarded and, at best, but a few remain applicable as safe and effective.

Without going into the advantages or disadvantages of using an artificial oxygenator, we may state that the concept of employing the lungs of the experimental animal or patient to be operated upon for their normal oxygenating purpose has always appealed to us as physiologically ideal. We have felt justified in exploring a number of possibilities through which this goal might be attained.

These investigations are not without precedent. The concept of autogenous lung oxygenation during cardiac bypass appears as a recurrent theme in the literature on this subject. Many of the early efforts directed at developing successful methods of bypassing the heart utilized pumps of various designs for the maintenance of circulation, and the autogenous lungs for the purpose of oxygenation. Thus, Gibbs,[1,2] Wesolowski and Welch,[3,4] Dodrill,[5,6] Sewell and Glenn,[7] and Kantrowitz,[8] all published accounts of successful experimental bypass of one or both sides of the heart in this fashion. On the other hand, the persistent efforts of Gibbon, Jr. and co-workers,[9,10] and the revolutionary application of low perfusion rates and bubble oxygenation by Lillehei,[11] DeWall,[12] and their associates, shifted the attention of many away from the employment of lung tissue and into the fertile field of oxygenator design and use. More recently, there have been sporadic attempts at reevaluating methods of autogenous lung oxygenation. Cohen, Warden and Lillehei[13,14] have reported on the successful experimental use of the temporarily isolated cardiac lobe of the dog for oxygenation during complete cardiac bypass using low perfusion flows. Again, Read, George, Cohen and Lillehei[15] pursued these efforts one step further and wrote on the use of the isolated left lung and open atrial drainage for the same purpose. Even more recently, Felipozzi, Santos and D'Oliveira[16] have engaged in experimental and clinical use of the autogenous lungs in bypass of the right heart for surgery of the pulmonic valve.

The present report concerns our experiences in the experimental laboratory during exploration of this problem and our search for a preparation that will provide adequate circumstances

* From the Mary Bailey Foundation for the Study of the Heart and Great Vessels and the Einstein Medical Center, Philadelphia.

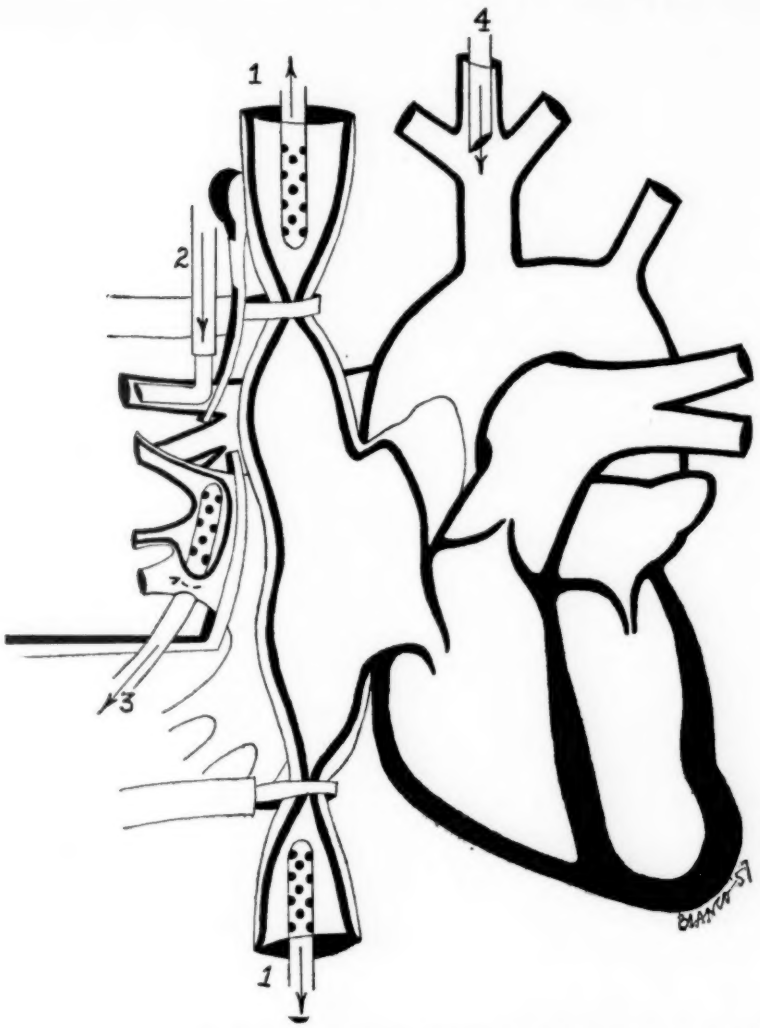


Fig. 1. Venous blood obtained from catheters in the venae cavae (1) is pumped into the upper lobe branch of the right pulmonary artery (2). Oxygenated blood from a "superior" pulmonary venous pouch (3) is pumped into the carotid artery (4).

for "open" intracardiac surgery. To this end we have employed varying amounts of pulmonary parenchyma for oxygenation, and different pump circuits to maintain the circulation during cardiac bypass. Finally, we wish to report on our first five clinical efforts with the use of the autogenous lung in complete circulatory bypass.

Method

Adult mongrel dogs weighing from 10 to 25 kg were anesthetized with sodium pentothal, intubated, and attached to mechanical respirators. Right thoracotomies through the fourth or fifth intercostal spaces were performed in all instances except when the left lung was to be employed as the "oxygenator." External jugular and femoral veins as well as the carotid artery were isolated and No. 14 Fr. plastic "oxygen" catheters were inserted into them in preparation for bypass. From here on the technics varied in the different series and will be described separately.

Series 1. Use of Autogenous Right Upper Lobe for Oxygenation During Bypass: Upon entering the chest the azygos vein was divided between liga-

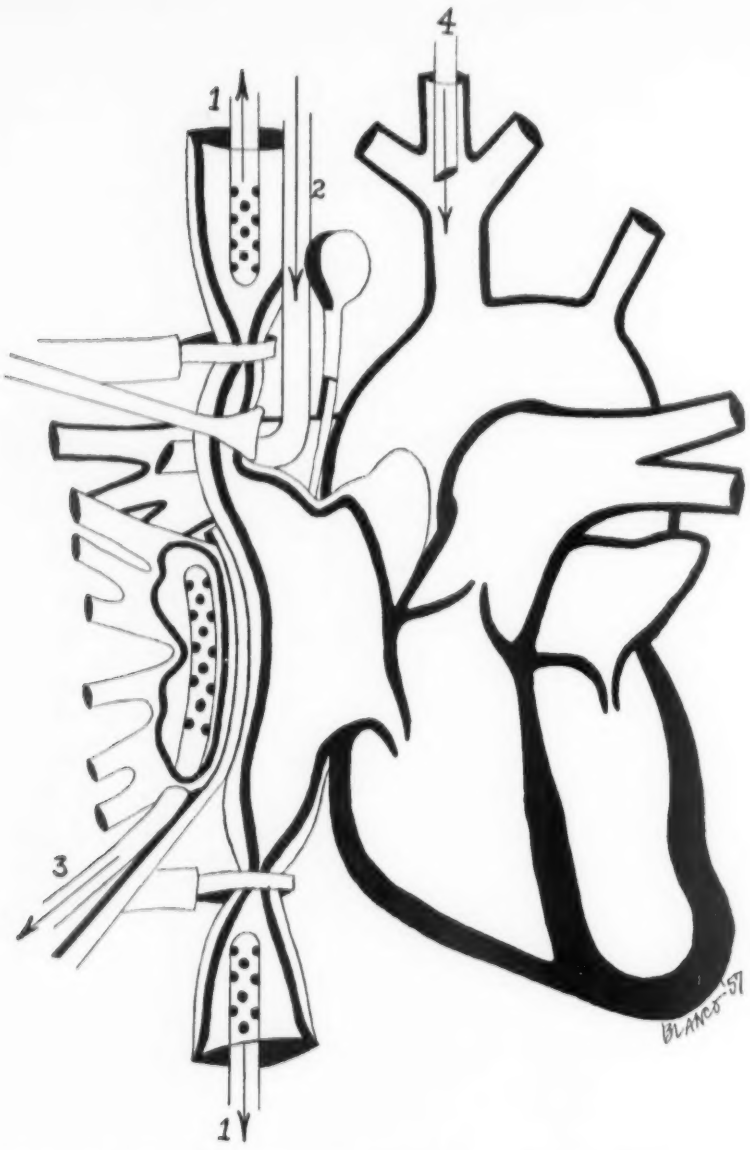


Fig. 2. Venous blood from catheters in the venae cavae (1) is pumped into the right (or left) pulmonary artery (2). Oxygenated blood from an isolated right (or left) pulmonary venous pouch (3) is pumped into the carotid artery (4).

tures and tapes were passed around the venae cavae. The upper lobe branch of the right pulmonary artery was dissected free, clamped at its origin with a serrefine or other suitable vascular clamp, and cannulated with a No. 14 Fr. "oxygen" plastic catheter. The superior "group" of right pulmonary veins was isolated and a small pouch was created from their common entrance into the left atrium (corresponding to the right superior pulmonary vein in the human). A curved Potts vascular clamp was applied to the base of this "pouch" and it was then cannulated with an appropriate plastic catheter. Proper connections were then established with tubing in a double Sigmamotor pump whereby blood from the caval catheters would be pumped into the catheter in the right upper lobe pulmonary artery, and oxygenated

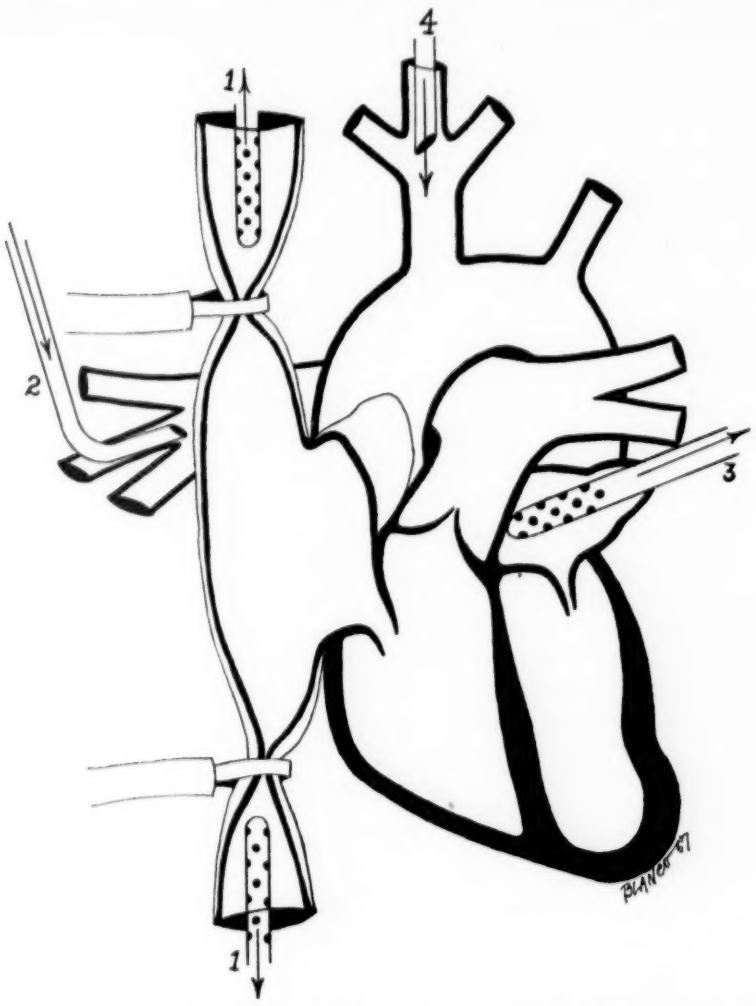


Fig. 3. Venous blood from catheters in the venae cavae (1) is pumped into a branch of the right pulmonary artery (2). The catheter points proximally. During bypass a clamp (not shown) is placed across the origin of the main pulmonary artery. Oxygenated blood from the left atrium (3) is pumped into the carotid artery (4).

blood from the pulmonary venous pouch was pumped into the carotid artery (Fig. 1).

Series 2. Use of Autogenous Right (or Left) Lung for Oxygenation During Bypass: A similar procedure to the one described was employed except that the right (or left) pulmonary artery was isolated and catheterized, and that a right (or left) atrial pouch was likewise dissected free and isolated so that after appropriate catheterization all of the right (or left) pulmonary venous drainage could be obtained and pumped into the right carotid artery (Fig. 2).

Series 3. Use of Both Lungs as Oxygenators During Bypass: After isolation of the venae cavae and ligation-division of the azygos, as described, a branch of the right pulmonary artery large enough to admit a No. 14 Fr. "oxygen" plastic catheter was selected and isolated near its origin. The plastic catheter was then introduced into it with its tip pointing proximally (Fig. 3) and secured in place. A No. 16 Fr. multiple hole plastic catheter was then introduced into the left atrium through the auricular appendage and placed in the atrium so that its tip reached but did not enter any of the right pulmonary veins. Blood would there-

fore be pumped from the cavae into the pulmonary arterial system (with the exclusion of that segment or lobe into whose artery the pulmonary arterial catheter was placed). After oxygenation the blood was picked up from the left atrium and delivered to the carotid artery. Before starting bypass the main pulmonary artery was clamped near its origin to prevent regurgitation of the blood pumped into it through the pulmonic valve and into the right ventricle.

Bypass Procedure: From this point the procedure was similar in all three series, as follows:

When bypass was to begin the tapes around the cavae were tightened and the pumps were turned on. With the exception of Series 1, flows were adjusted to 50 ml/kg/min. Immediately after verifying that the pumping system was working well, the right ventricle was opened and kept open for 15 to 30 min after which time the ventriculotomy was closed. The pumps were then slowed down and stopped before the last closing stitch was placed to prevent distension of the right ventricle with coronary venous blood. The pulmonary artery clamp was released (when it had been used). After making sure that good cardiac action was present all catheters and clamps were removed, the incisions in the pulmonary vessels and atria were sutured, and the chest was closed in layers leaving an indwelling catheter for suction drainage. Penicillin was administered in dosages of 600,000 units after operation and daily for four days thereafter.

Pump Circuits Employed: Double Sigmamotor* pumps (model TS6) were used throughout. A blood reservoir was incorporated into the afferent limb of the "venous" pump head for replacement of blood lost during ventriculotomy. A depulsator was incorporated into the tubing leading to the pulmonary artery (or its branches). A filter-bubble trap was placed in the afferent limb of the arterial pump head.

Use of Heparin: The blood used in priming the tubing and reservoir was obtained from donor dogs the day of the experiment. It contained 4 mg of heparin per liter. In experiments employing the pump circuits described above no heparin was used in the animal to be operated upon. In recent experiments (to be mentioned briefly below) we have administered heparin in dosage of 2 mg/kg of body weight.

* Sigmamotor Inc., Middleport, N. Y.

Experimental Results

Many experiments were undertaken to perfect various technics and try out different pump circuits. The results reported below are from experiments in which long term survival was attempted.

Series 1: In 16 consecutive dogs the right upper lobe was used for purposes of oxygenation. In ten of these animals pump flows between 25 and 35 ml/kg/min and periods of bypass between 15 and 25 min were employed. All dogs survived the operation and nine remained normal for over two weeks after the cardiotomies at which time they were sacrificed. One dog showed signs of cerebral damage with sluggish behavior, blindness, and localized convulsive movements which persisted for ten days when he was sacrificed. In the remaining 6 dogs flows between 35 and 65 ml/kg/min were used and the bypass periods were extended to 30 min. All these dogs died within 48 hours of operation. All exhibited varying degrees of pulmonary edema as evidenced by pink watery drainage from nostrils and mouth and autopsy findings of congestion and edema of pulmonary parenchyma. The findings were most severe in the right upper lobe but also were present in the adjacent lobes.

Series 2: In 11 consecutive dogs the right (or left) lung was employed as oxygenator. Flows of 50 ml/kg/min were employed for an average bypass time of 30 min. Considerable difficulty was experienced in obtaining adequate drainage of the isolated atrial pouches in these animals. The irregular shape and soft walls of these pouches made closed suction drainage with indwelling catheters susceptible to collapse of the atrial wall around the catheter with intermittent plugging and interruption of drainage. Six dogs died in the immediate postoperative period and, in all, severe degrees

of pulmonary edema and congestion were evident before death and at autopsy. The remaining five dogs survived for two weeks after the procedure and were sacrificed. Autopsy revealed essentially normal pulmonary parenchyma although adhesions were common and in one instance there was evidence of a localized empyema as ociated with wound infection.

Series 3: In 13 consecutive dogs both lungs were employed in their normal oxygenating capacity during bypass. Flows of 50 ml/kg/min were used and bypass was maintained for 30 min. All dogs survived the procedure but three died within 72 hours of the operation from causes unrelated to the bypass or to the employment of autogenous lung oxygenation. In one, the chest drainage catheter became dislodged causing death from massive pneumothorax. In another, the ligature employed to close the left atrial incision slipped, the animal died from hemorrhage and atelectasis. A third dog died on the second postoperative day from distemper that apparently was unnoticed before operation. Of the survivors, those that have been sacrificed and autopsied have shown essentially normal pulmonary parenchyma.

Discussion of Experimental Results

From the foregoing it seems that an isolated lobe is a satisfactory oxygenator as long as its circulatory capacity is not exceeded by high flows. These may produce within its capillary circulation pressures higher than the oncotic pressures of the plasma proteins and result in edema. On the other hand, very low flows tax the physiologic reserves of the animal. In our first series arterial blood pH values were consistently low (ranging between 6.9 and 7.1). Again, although arterial oxygenation appeared adequate (mean values of 93 per cent oxygen saturation), perfusion with such low flows may be near the tolerance level of such tissues as the brain.

With regard to our attempts to employ one or the other lung for oxygenation it appears that in the dog, at least, the anatomic configuration of the pulmonary venous drainage channel does not lend itself well to isolation of an atrial pouch and closed catheter drainage of its cavity. These difficulties were encountered and reported by Read, George, Cohen and Lillehei[15] who finally resorted to suturing soft Penrose drains to the atrial wall, thereby providing for open drainage of the isolated atrial pouch.

Our best results were obtained in our third series and we have recently extended our observations with this preparation to experimental situations that resemble conditions that might be encountered clinically. We refer to the creation and closure of interventricular septal defects and to direct surgery upon the aortic valve. Both of these situations provide circumstances under which an indirect communication exists between the left atrium (where we have placed our collecting catheter) and the operative field. We have been especially interested in ascertaining whether severe blood loss would result. These procedures have been carried out under potassium citrate arrest in heparinized animals. By increasing the rate of the pump attached to the atrial line, blood loss through artificially created interventricular septal defects or through the aortic valve (in direct valve surgery) can be controlled completely. Under these conditions there exists the possibility that air might be sucked into the atrial line and gain access to the "arterial" tubing leading to the carotid artery. This problem has been solved by interposing an extra pump head between the atrial catheter and a reservoir for the arterialized blood. From this reservoir the blood is picked up by the "arterial" pump head and injected into the carotid artery.

Clinical Applications

As a result of these promising experiences in the animal laboratory it was decided to try a modification of the method employed in Series 3 clinically. A bubble-type oxygenator, which previously had been used in this type of case was incorporated in the perfusion circuit in such a way that the autogenous lungs could readily be "cut out" of the system and replaced by the oxygenator should any difficulty in oxygenation or perfusion develop. The circuit employed is shown in Figure 4.

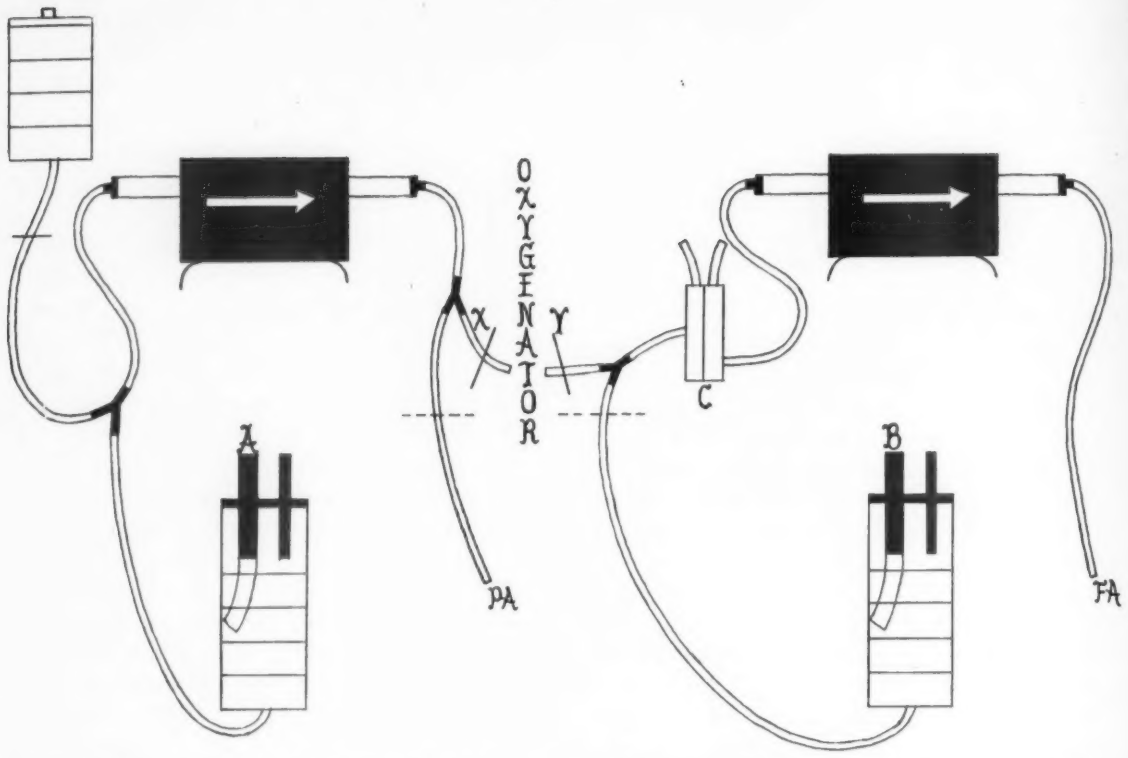


Fig. 4. Extracorporeal circuit: Venous blood from the right atrium drains by gravity into reservoir A, from which it is pumped into the pulmonary artery. Oxygenated blood from the left atrium drains by gravity into reservoir B and after passing through bubble trap C is pumped into the femoral artery (FA). Clamps at X and Y separate an artificial oxygenator from the circuit. Should a change to its use be deemed advisable they are shifted to the positions indicated by the broken lines.

It was felt that our first trials should be in adult patients with aortic valve disease because of the relative consistency of the pathology and the large size of the structures involved. Further it was felt that the long periods of bypass which frequently are required to correct these lesions would put the method to a more complete test. We present below our surgical experience in four cases of aortic stenosis and one case of aortic insufficiency.

Case Histories

Case 1. E.S., a 57-year-old white man, was admitted to Hahnemann Hospital on August 12, 1957 with chief complaints of pain in the chest, choking sensation, and dyspnea on exertion for the past three years. The patient, a resident of South Africa, had noticed the onset of the above symptoms and gradual progression of the same until on admission his activity was markedly limited. He was suffering from three-pillow orthopnea and had started to notice moderate swelling of the ankles especially after prolonged standing. There had been occasional episodes of paroxysmal nocturnal dyspnea associated with the chest pain during the previous six months.

Physical examination revealed moderate enlargement of the heart by percussion. A grade 3 harsh systolic murmur was heard at the base of the heart and was transmitted to the neck and apex. A_2 was absent. There was 2 plus ankle edema. Electrocardiogram revealed sinus rhythm with marked evidence of left ventricular hypertrophy and strain. Chest x-ray showed slight left ventricular enlargement associated with aortic valve calcification.

Combined heart catheterization on August 15, 1957 showed the left ventricular pressure to be 230/7. Simultaneous brachial artery pressure was 112/58 with a peak to peak gradient across the aortic valve of 118 mm Hg.

Diagnosis of aortic stenosis, severe, causing coronary insufficiency was made and open aortic commissurotomy was advised.

Operative Procedure: On August 21, 1957 the patient underwent a division of aortic commissures and dilatation of the aortic valve orifice by an open technic. The extracorporeal circuit employed was as follows: No. 28 Fr. plastic catheters inserted in each vena cava drained

venous blood by suction provided by a Sigmamotor pump head and the latter injected this blood into the pulmonary artery through a catheter placed in the right ventricular outflow tract and across the pulmonic valve. A tape had been previously passed around the main pulmonary artery to be tightened around this catheter at the onset of bypass. A No. 40 Fr. plastic catheter was placed in the left atrium and drained arterialized blood by suction provided by a second pump head which, in turn, pumped this blood into an arterial reservoir. From here the oxygenated blood was picked up by a third pump head and injected into the subclavian artery. A bubble type oxygenator (Friedland-Gemeinhardt) was connected to the circuit and held in readiness to be incorporated in it should any difficulty arise with the use of the autogenous lungs.

Shortly after initiation of bypass the ascending aorta was cross clamped and a 2.5 per cent solution of potassium citrate in blood was injected proximally to obtain cardiac arrest. The ensuing aortotomy and the valvular manipulations were performed on the quiescent heart.

Autogenous lung bypass was maintained 36 min and appeared satisfactory in all respects. On removal of the aortic cross clamp, ventricular fibrillation developed. Because of lack of experience in the use of this special method of perfusion we felt it was advisable to shift to the use of the oxygenator at this point, and did so with re-establishment of normal rhythm after a single electric shock. Bypass on the oxygenator lasted 10 min. Induced cardiac arrest lasted 30 min. The rest of the procedure was uneventful.

Postoperative Course: The early postoperative course was characterized by considerable bloody drainage from the right thoracic cavity. Six hours after the initial operation the bilateral anterior thoracotomy employed originally was reopened and a site of leakage in the aortic incision was repaired, thus controlling the hemorrhage. After this the patient's course in the hospital was satisfactory and he was discharged on September 11, 1957.

He spent the next six weeks convalescing at a local nursing home. On October 8, 1957 the patient was readmitted for combined heart catheterization studies. He exhibited marked subjective and objective improvement. There was considerable reduction in the exertional dyspnea and complete disappearance of the anginal pain. On physical examination the aortic systolic murmur was found to be diminished in intensity when compared with the preoperative findings. Catheterization revealed left ventricular pressure to be 160/6. Simultaneous brachial artery pressure was 118/65 with a gradient across the aortic valve of 42 mm Hg.

Convalescence from cardiac catheterization was uncomplicated and he was discharged on October 12, 1957 to return to his home in South Africa.

Case 2. H. G., a 55-year-old white man, was admitted to Hahnemann Hospital on February 10, 1958 with a chief complaint of shortness of breath and fatigue on exertion of four years' duration. Although a careful history failed to reveal any recollection of an acute rheumatic episode the patient had been told he had a heart murmur in 1925. No complaints referable to the heart appeared until 1954 when the above mentioned exertional dyspnea and fatigue began and progressed gradually. There was no history of syncope, chest pain, or peripheral edema.

On physical examination the pertinent findings were limited to the heart which showed a grade 3 aortic systolic murmur with absence of the aortic second sound.

Left heart catheterization done on February 8, 1958 showed the left ventricular pressure to be 188/13 while simultaneous brachial artery pressure was 137/67. The peak to peak gradient across the aortic valve was 51 mm Hg.

A diagnosis of aortic stenosis was made and the patient was discharged on February 21, 1958 with a recommendation that he return for open aortic commissurotomy.

He was readmitted on March 2, 1958 and scheduled for surgery on March 4th but 12 hours prior to operation he developed bigeminal rhythm which was thought to be due to digitalis effect and the operation was postponed 48 hours.

Operative Procedure: On March 6, 1958 an open aortic commissurotomy and "sculpturing" of two of the valve cusps was performed employing the patient's own lungs as oxygenators. A bilateral anterior thoracotomy was performed. The extracorporeal circuit included the following: A #38 Fr. plastic catheter was inserted into the right atrium and drained the venous blood by gravity through $^{7}/_{16}$" I.D. Tygon tubing into a reservoir placed about 40 cm below table level. From this reservoir the blood was pumped by a Sigmamotor pump head into the pulmonary artery through a #28 Fr. catheter placed through a stab wound in the right ventricular outflow tract and past the pulmonic valve. (An umbilical tape was previously placed around the main pulmonary artery to be tightened around this catheter during bypass.) Another #38 Fr. catheter was inserted into the left atrium and drained oxygenated blood by gravity into a second dependent reservoir. From here a second Sigmamotor pump head injected it into a catheter which had been inserted into the right femoral artery.

A bubble oxygenator (Friedland-Gemeinhardt) was connected to the circuit and held in readiness to be incorporated should any difficulty arise with the use of the autogenous lungs or during the period of re-establishment of independent heart action. This proved unnecessary.

Shortly after initiating the bypass the aorta was cross clamped about 6 cm above its origin and a 2.5 per cent solution of potassium citrate in blood was injected proximally to obtain cardiac arrest. A generous aortotomy was then performed and the aortic valve commissures incised widely, providing an adequate orifice. Considerable amounts of calcium were removed from two of the valve cusps, restoring most of their flexibility.

After these manipulations the aortotomy incision was closed, and the aortic cross clamp released. Heart beat was resumed 50 sec after release of the aortic clamp.

The heart had been arrested for 50 min. During the next 10 minutes cardiac contractions strengthened and the pumps were stopped after 62 min and 45 sec of initiating the bypass. Flows during bypass had averaged 60 cc/kg/min.

Postoperative Course: The patient appeared fully conscious and reactive very shortly after the procedure ended. Hematologic and coagulation studies at this time revealed values which were notably close to normal. Plasma hemoglobin was reported as 15.0 mgm % and platelets at 150,000/cu mm immediately after bypass.

The postoperative course remained uneventful except for the reappearance of bigeminy for a short time during the second postoperative day. On this same day it was felt that the patient was not coughing effectively and a tracheotomy was performed to facilitate tracheobronchial aspiration. The patient's condition remained satisfactory after this.

Case 3. H. C., a 50-year-old white man, was admitted to Hahnemann Hospital on February 23, 1958 complaining of precordial pain and fatigue of six months' duration. A heart murmur had been discovered in 1948 but the patient remained asymptomatic until September 1957 when the above symptoms appeared and progressed relatively rapidly. During the last months he had also noticed dizziness and shortness of breath on moderate exertion. No definite history of an acute rheumatic attack could be elicited.

On physical examination a grade 3 rough systolic murmur was heard over the aortic area. A_2 was barely audible.

Left heart catheterization showed the left ventricular pressure to be 196/9, and the brachial artery pressure 119/63 with a peak gradient across the aortic valve of 77 mm Hg.

The electrocardiogram showed left ventricular hypertrophy and strain with ischemic changes of the inferior wall of the left ventricle.

A diagnosis of dynamic aortic stenosis was made and open aortic commissurotomy and "sculpturing" of the aortic cusps was advised. This was performed on March 7, 1958.

Operative Procedure: The cannulations and extracorporeal circuit were identical to those employed in case 2. Elective cardiac arrest was used and lasted 39 minutes. Adequate opening of the aortic valve orifice was obtained. Ventricular fibrillation followed the release of the aortic clamp but responded promptly to a single electric shock. Cardiac bypass was maintained for a total of 63 minutes.

Postoperative Course: The postoperative course was very satisfactory, the only complication arising on the third postoperative day when the temperature rose to 104° F. This rise was interpreted as due to partial atelectasis and a tracheotomy was performed. The fever subsided promptly after thorough tracheobronchial aspiration and an uneventful course followed.

Case 4. A. H., a 48-year-old white man, was admitted to Hahnemann Hospital on February 20, 1958 with chief complaints of shortness of breath and chest pain of two months' duration. He gave a history of rheumatic fever at six years of age from which he recovered apparently completely so that during adolescence and early adulthood he engaged in strenuous sports without difficulty. In 1930, a heart murmur was discovered but he remained asymptomatic until January 4, 1958 when he experienced sudden pain in the chest lasting for 10 to 15 minutes, followed by a coughing spell and shortness of breath. He was examined by a local physician who told the patient he was in cardiac failure, placed him on bed rest for five weeks and prescribed digitalis and mercurial diuretics. Since then the patient experienced dyspnea on exertion and had to limit his activities markedly.

On examination there was a harsh grade 3–4 systolic murmur heard all over the chest but more so over the aortic area. There was an early blowing diastolic murmur heard along the left sternal border. A_2 was absent and P_2 was diminished.

Combined heart catheterization performed on February 24, 1958 showed left ventricular pressure to be 238/23. Simultaneous brachial artery pressure was 121/64 with a peak to peak systolic gradient across the aortic valve of 117 mm.

Electrocardiogram showed sinus rhythm with portions of the record showing first degree block and others showing partial A-V block.

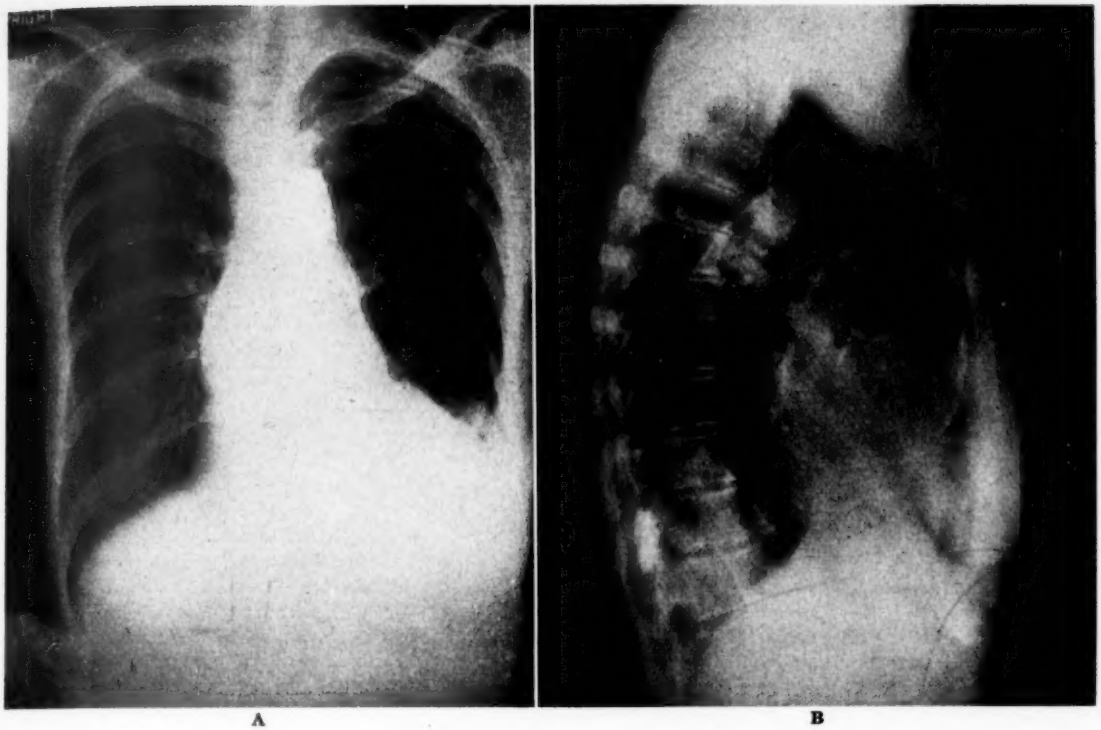
A diagnosis of aortic stenosis and adynamic aortic insufficiency was made and open aortic commissurotomy and sculpturing of the cusps was advised.

Operative Procedure: Operation was performed on March 14, 1958. The autogenous lungs were used for oxygenation and the extracorporeal circuit was the same as described for case 2. Total cardiac bypass time was 82 min and 12 sec. The heart was arrested with potassium citrate for 67 min. Upon release of the aortic clamp the heart which had started beating weakly, developed ventricular fibrillation and was successfully restored to normal rhythm after two electric shocks. During arrest an aortic commissurotomy was performed with removal of large amounts of calcific deposits from the cusp surfaces rendering the latter pliable and so *lengthening* them that they became competent once more.

Hematologic values after bypass were normal. Blood pressure before bypass was 115/70. Ten minutes after bypass it had attained a level of 130/80 which was maintained thereafter.

The postoperative course was uneventful.

Case 5. H. B., a 58-year-old white woman, was admitted to Hahnemann Hospital on March 2, 1958 with chief complaints of intermittent attacks of shortness of breath and of "blacking out" of two years' duration. She gave a history of a heart murmur discovered when she was 19 years old, and of lues diagnosed and treated with penicillin in 1942. Severe "rheumatic" pains appeared in the same year and necessitated complete bed rest. Since that time she experienced occasional attacks of shortness of breath and fainting upon exertion.



A B

Fig. 5. Case 5. PA and lateral roentgenograms of case 5 showing dilatation of the supravalvular and ascending aorta and extensive calcification of the aortic wall.

In November 1957 she suffered an episode of severe dyspnea followed by ankle edema and pleural effusion treated with bed rest, digitalis, and mercurials.

The only other complaint was of intermittent attacks of mucous colitis during the past four years.

Physical examination showed her to be in moderate distress because of dyspnea and orthopnea. Blood pressure was 180/0. There was engorgement but no pulsation of the neck veins. The chest was clear on admission but the liver edge was felt one finger's breadth below the right costal margin. Auricular fibrillation and a grade 3 diastolic murmur were present.

Chest x-rays showed slight pulmonary emphysema and fibrosis with slight generalized cardiac enlargement. Moderate to marked dilatation of the aorta was present and the vessel showed severe calcification throughout its extent (Fig. 5A, B).

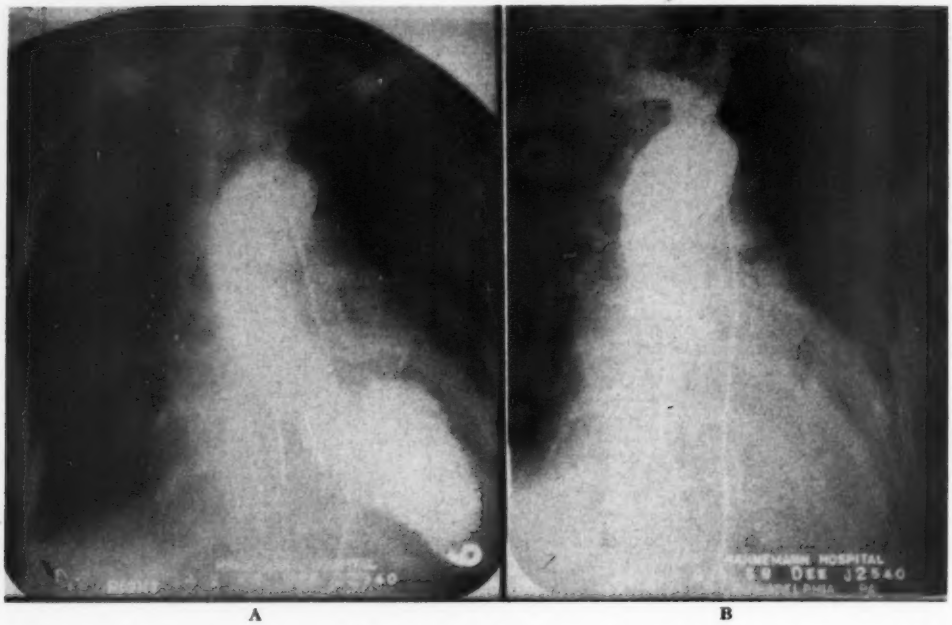
The Kolmer test was slightly positive.

The electrocardiogram showed auricular fibrillation with a well controlled ventricular response. Myocardial damage, combined heart strain, and digitalis effect were also in evidence.

Although the patient experienced weight loss under a cardiac regime she continued to reaccumulate fluid in both pleural spaces and had to be tapped repeatedly. At thoracentesis amounts ranging from 500–1,000 cc of clear straw colored fluid were removed.

Operative Procedure: On March 19, 1958 an open repair of aortic insufficiency and resection of one-third of the circumference of the ascending portion of the aorta was carried out. Valvular repair consisted of resection of the non-coronary cusp and conversion of the aortic valve into a bicuspid structure by plication of the aortic wall at the valvular level. The resected, pliable cusp was sutured to reinforce one of the remaining cusps which was somewhat distorted in order to attain secure valvular closure during diastole.

The extracorporeal circuit employed was identical to the one described in case 2. Bypass employing the autogenous lungs lasted for 1 hour and 50 minutes. The heart was arrested with an injection of potassium citrate during 1 hour and 37 min. Upon release of the aortic cross clamp after closure of the aortotomy the ventricles fibrillated but the heart was restored to normal forceful beat after one electric shock. At this time it was noted that the previously present systolic and diastolic thrills were diminished markedly. The catheter employed to inject blood into the pulmonary artery was then removed and the stab wound in the right ventricular outflow tract repaired. Accompanying these manipulations it was seen that cardiac contractions faltered and fibrillation reappeared. Several alternatives in treatment offered themselves and it was decided to place quickly the bubble oxygenator "in" the extracorporeal circuit before attempting defibrillation. This was done and the heart was successfully restored to normal rhythm after three electric shocks. This second bypass period on the mechanical pump-oxygenator



A B

Fig. 6. Case 5 (A). Postoperative ventriculogram showing correction of aneurysmal dilatation by resection. (B) Postoperative ascending aortogram showing competence of the aortic valve.

lasted 22 minutes. After this the heart maintained a good output with a blood pressure of 170/80 which became stable and has been maintained to date. Total bypass time was two hours and twelve minutes.

Postoperative Course: The postoperative course was uneventful except for tracheotomy performed on the second postoperative day to facilitate tracheobronchial aspiration.

Postoperative aortography and ventriculography showed dramatic results with respect to aortic contour and to competence of the aortic valve (see Fig. 6A, B). Records of the patient's blood pressure are shown in Figure 7 and demonstrate the prompt postoperative return of diastolic pressure to normal values and the shrinkage of the pulse pressure due to regained valve competence. The more gradual reduction in systolic pressure is also gratifying.

Comment

Encouraged by our experimental results we have applied the principle of autogenous lung oxygenation to clinical cardiac bypass. In the first five clinical tests, a minimum of trouble was experienced during operation. Flow rates in each case were higher than would have been possible with our oxygenator. The level of blood oxygenation was always above 93 per cent of saturation. At the termination of each perfusion platelet counts equaled or exceeded preperfusion levels and plasma hemoglobin values did not rise above 20 mg %. These findings are significant in view of the length of the perfusion periods (36 min to 110 min) and the high flows (all above 4,000 cc/min) employed. In two instances the bubble oxygenator was substituted for the autogenous lungs at the termination of the initial perfusion period, being used for 10 and 22 min, respectively.

It is our feeling that the use of the autogenous lungs for oxygenation of the blood during cardiac bypass is worthy of much wider clinical trial. Certainly the damage to blood elements which is inherent in the use of total cardiopulmonary bypass occurs mainly in the oxygenator rather than in the pumping mechanism. Hence, it would seem that much longer periods of bypass would be feasible with the autogenous lungs than with any of the existing oxygenators. This increased permissible time limit would be especially helpful in surgery for acquired aortic stenosis or insufficiency not only because of the complexity of the time-consuming corrective measures, but also because restoration of an effective independent heart beat may take considerable time.

The operative mortality with total cardiopulmonary bypass increases greatly and progressively after the first 60 min largely due to the damage imparted to blood elements and to

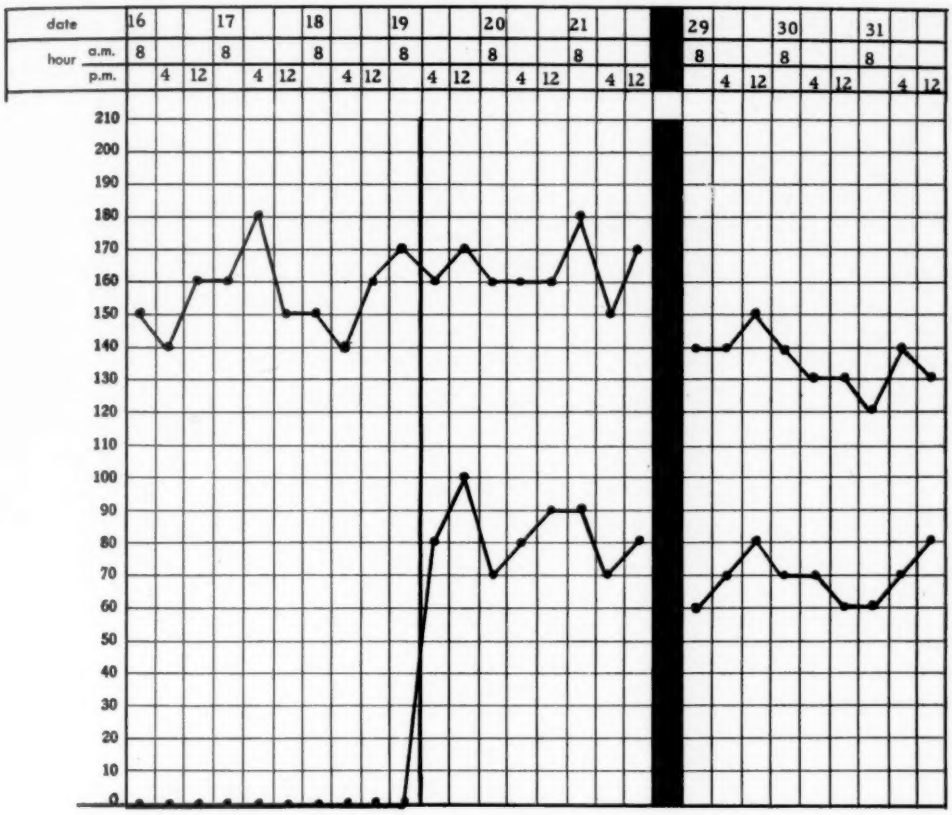


Fig. 7. Case 5. Records of arterial blood pressure indicating prompt changes in diastolic and pulse pressures after correction of insufficiency at operation, and more gradual return of systolic blood pressure to normal levels.

other cumulative phenomena associated with extracorporeal oxygenation. Since these factors are reduced with the use of autogenous lung oxygenation one would expect to obtain higher survival rates with this new method in longer operative procedures.

Summary

A study was undertaken to assess the applicability of autogenous lung oxygenation during cardiac bypass. The results of the experimental employment of varying amounts of pulmonary parenchyma for this purpose have been presented. Clinically, the method has been applied successfully to the surgical treatment of aortic valve disease. Five such cases are reported.

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Direct Surgical Relief of Coronary Artery Occlusion*

LEONARD GOTTESMAN, M.D.

Cincinnati, Ohio

FOR MANY years the surgical approach to treatment of myocardial ischemia was devoted to developing new channels for blood supply to the myocardium. This approach naturally followed definition of the basic problem as ischemia secondary to coronary artery occlusion. Accepting occlusive atherosclerotic arterial disease as irreversible, investigators turned to indirect methods of "revascularization." Scarification of the epicardium; irritating foreign bodies; muscle, lung, and other tissue grafts; ligation and/or arterialization of the coronary sinus; and intramural implants of systemic vessels are some of these suggested methods. More recently, the concept of selective potential of the surface of the heart and its relationship to ventricular fibrillation has gained attention.

The magnitude of the problem of occlusive coronary artery disease has not permitted an easy answer, but continues to stimulate the search for a direct and effective alleviation of the myocardial ischemia.

PATHOLOGY OF CORONARY OBSTRUCTION

The morbid anatomy of coronary occlusion offers good basis for the belief that direct restoration of coronary arterial flow is possible.

It has been established that intercoronary anastomoses measuring 40 to 200 micra in diameter develop in those hearts with deficient arterial blood supply. Because of these anastomoses, the right coronary artery may nourish the left ventricle, as may either of the main branches of the left coronary artery. Hence, if coronary obstruction develops slowly, the development of these anastomoses invalidates the "end-artery" concept of coronary arterial distribution. Further, because of these anastomoses, re-establishment of flow through any of the main coronary arteries should add significantly to nourishment of the left ventricular wall.[1]

In 1941, a study of 400 human hearts—autopsy specimens—demonstrated two pertinent facts. First, most zones of occlusion in the coronary arteries are less than 5 mm in length. Second, the majority of such occlusions are within 4 cm of the mouths of these vessels[2] (Fig. 1).

With recognition of the pathology of coronary artery disease as obstruction rather than obliterative occlusion came the obvious thought that surgery of amenable obstruction elsewhere has led to dramatic achievement. This has held true for the biliary tract, the bronchial tree, gastrointestinal tract, the urinary tract, the vascular tree, and for obstruction within the heart. Since, in recent years, surgery of peripheral arterial obstruction has been so successful,[3] direct surgical relief of coronary artery obstruction appears worthy of investigation.

SURGICAL METHODS FOR RELIEF OF ARTERIAL OBSTRUCTION

Relief of obstruction in peripheral arteries is accomplished by one of two methods. Endarterectomy is one, bypass or replacement of the obstructed segment is the other. For this second technic, vein, artery, and plastic prosthesis have all proved effective, and the technics have reached a high degree of efficiency. Note-

* From the May Institute for Medical Research, Cincinnati, Ohio.

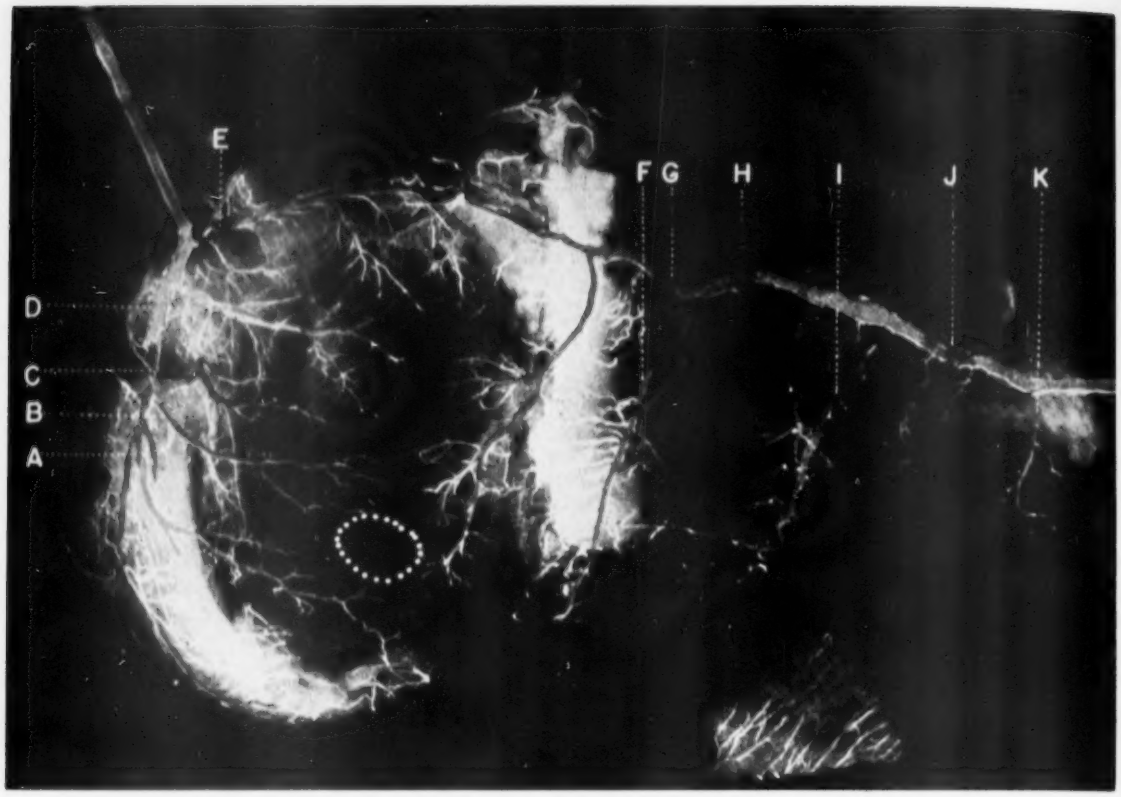

Fig. 1. Injected and unrolled heart. A, B, C, D, E, F, I, K—complete occlusions. G, H—emboli. J—fresh thrombus. (Reproduced from Blumgart, H. L., *et al.*: *Am. Heart J.* 19: 1, 1940, C. V. Mosby Co., St. Louis, Mo. Published by permission of the authors and publisher.)

worthy in the evolution of these operations has been the gradual abandonment of endarterectomy in favor of the bypass operations by the majority of vascular surgeons. It is true that Cannon and Barker have not followed this trend,[4] and they remain strong advocates of extensive thromboendarterectomy.

Operations designed to bypass arterial obstruction have gained favor with some reason. First, there is no interference with existing patent vascular channels. Second, a widely patent anastomosis can more easily be attained. Endarterectomy, on the other hand, leaves a shaggy inner arterial wall, which, particularly in smaller vessels, has a tendency to promote thrombosis. Further, the point of distal dissection of the intima leaves a shelf which can loosen and form an obstructing flap within the lumen. This again predisposes to postoperative thrombosis.

Drawing upon experience with peripheral arterial atherosclerosis, circumvention of obstruction is best obtained by end-to-side anastomosis of the new source of blood supply to the afflicted vessel beyond the point of obstruction.[5] Endarterectomy has generally given disappointing results.[6]

The preceding, then, constitutes the basis for investigating the possibility of direct surgical relief of obstructive coronary arterial disease. This attack may involve introduction of blood flow beyond the obstruction or removal of that obstruction.

Direct Surgery for Coronary Obstruction

The coronary arteries do not offer entirely the same problems as the peripheral arteries even though the arterial pathology in atherosclerosis is the same. The difficulties with direct attack on the coronary arteries arise from the normally continuous myocardial contractions

and the normal need of the myocardium for uninterrupted blood supply.

During recent months, following observations described by Absolon,[7] experience in the autopsy room has repeatedly demonstrated the feasibility of endarterectomy of extensive portions of the main coronary vessels. This can be accomplished by laying open the artery, or by stripping the endarterial plaques through multiple small incisions (Fig. 2).

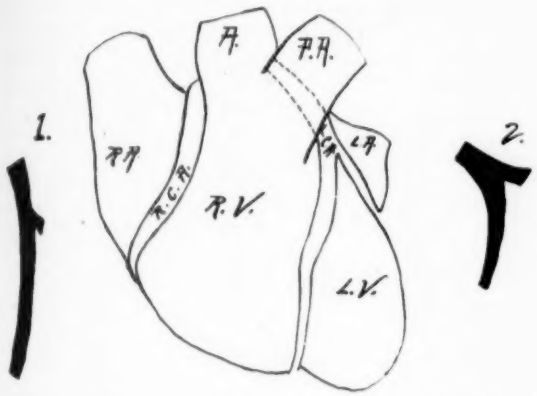

Fig. 2. Diagrammatic sketch of casts removed from coronary arteries at autopsy. (1) Cast of right coronary artery. (2) Cast of left coronary artery.

The work referred to above, as well as a somewhat more extensive study recently reported,[8] also described successful end-to-end anastomoses between the internal mammary artery and the circumflex coronary artery in the dog. Both reports demonstrate that technical ability permits completion of the anastomosis without arresting cardiac activity. The difficulties were such, however, that one report suggested the use of an extracorporeal pump oxygenator, and the other reported such use in a group of seven dogs.

EXPERIMENTAL APPLICATIONS

Experimental verification of such accomplishment was undertaken. Using a group of five dogs, end-to-side anastomosis of the left internal mammary artery to the left circumflex coronary artery was carried out. The operations were performed in normothermic dogs under general anesthesia. A temporary shunt for coronary blood supply was used (Fig. 3). Three dogs died of ventricular fibrillation, and the remaining two survived. One of these, autopsied four weeks later, showed a patent anastomosis (Fig. 4). The other has not yet been sacrificed.

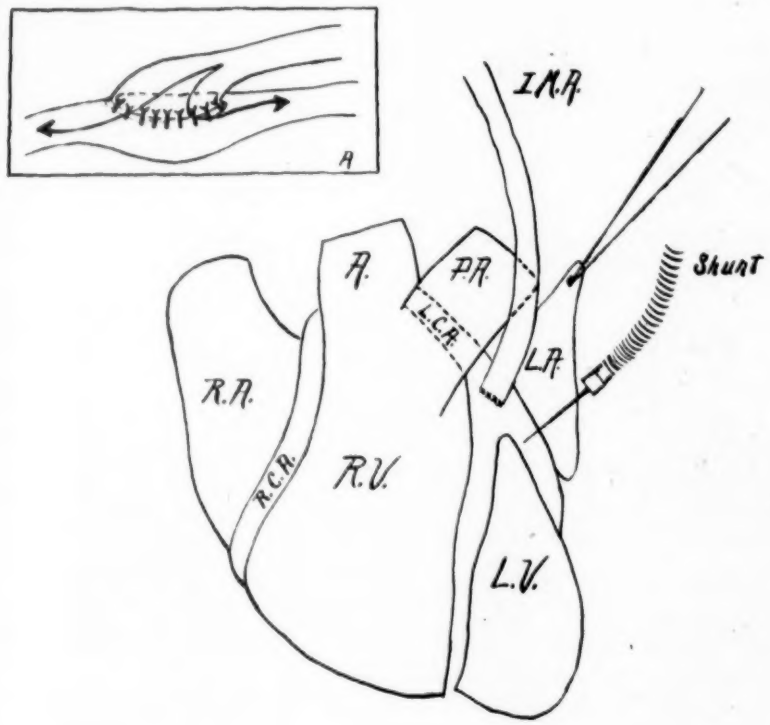

Fig. 3. Diagrammatic sketch of end-to-side anastomosis between internal mammary artery and left coronary artery. Inset shows detail of end-to-side anastomosis with bidirectional flow.

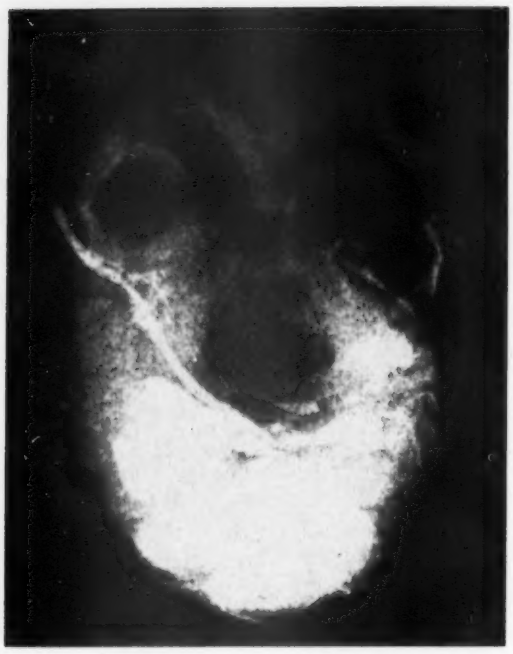

Fig. 4. End-to-side anastomosis between internal mammary artery and left coronary artery. Autopsy specimen of dog's heart four weeks postoperative, injected with aqueous Dionosil® and x-rayed.

Although far from conclusive, this small study does indicate the feasibility of using bypass technics to restore blood flow to coronary arteries beyond points of obstruction.

Reason indicates that extra-corporeal pump oxygenators are necessary to further the technic, particularly if attempts at human application are made. The pump oxygenator will serve to maintain homeostasis while presenting the surgeon with a quiet surgical field.

Clinical Applications

Coronary Angiography: Human application will also entail anatomically accurate diagnosis of coronary artery obstruction. Peripheral angiography has long been used to map out peripheral arteries with delineation of patent and occluded areas. Functioning anastomatic channels are demonstrated as well. Fortunately, similar and safe visualization of the coronary arterial tree, if not already, will soon be available[9,10] (Fig. 5, 6).

Using 90 per cent Hypaque®, the Bailey Thoracic Clinic has done 40 coronary artery

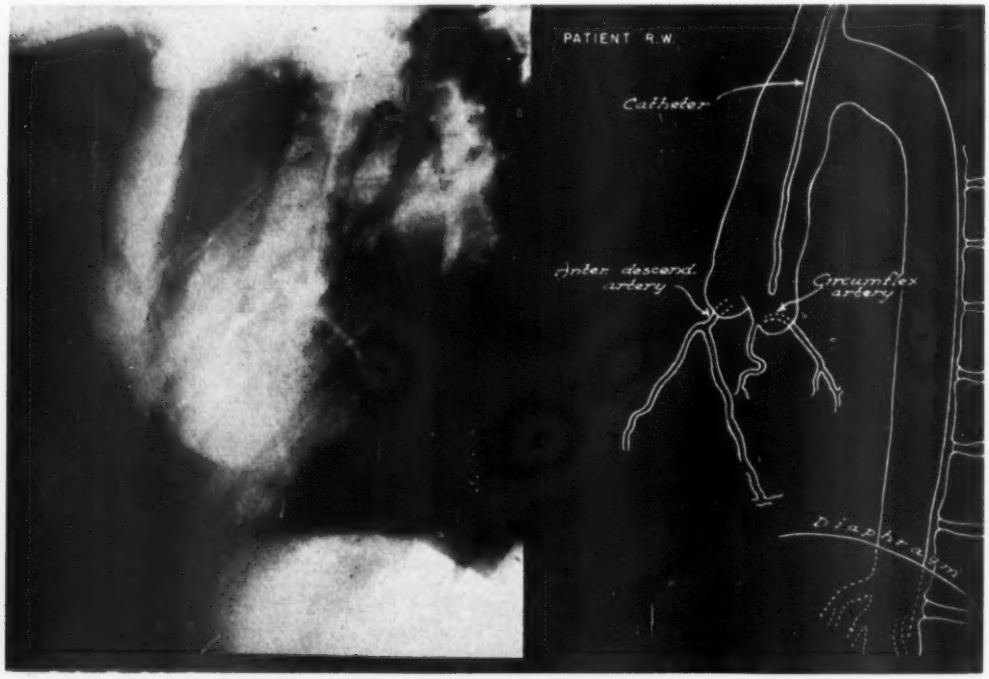

Fig. 5. Coronary arteriogram. Right posterior oblique and line tracing. Demonstration of circumflex and anterior decending artery. (By permission of B. Felson, Professor of Radiology, University of Cincinnati.)

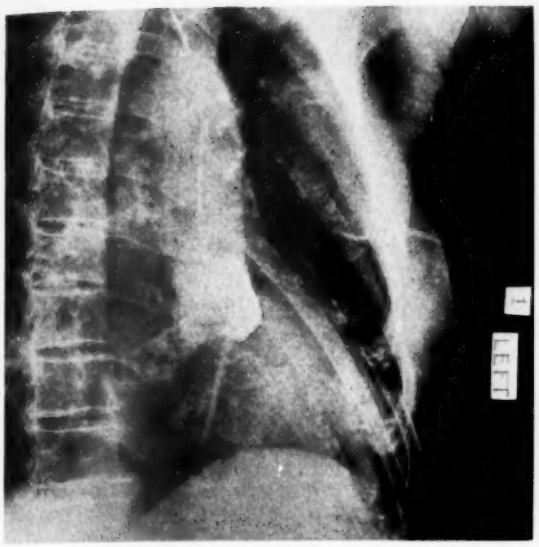

Fig. 6. Coronary arteriogram showing obstruction of entire left coronary arterial system. Left ventricle nourished by right coronary artery. (By permission of B. Felson, Professor of Radiology, University of Cincinnati.)

mappings, without mortality. The technic employs direct aortic puncture, using the suprasternal approach. Under observation, the needle is advanced to the level of the aortic valve, and using a pressure mechanism, rapid injection of 45 cc of contrast medium is made. Recently, acetylcholine in 25 mg doses has been used to slow or momentarily stop cardiac activity. Excellent coronary filling is obtained.

That coronary angiography is needed for the present relates this type of surgery to other cardiovascular diseases which forced the clinician to extend his diagnosis to the point of accurate cartography, reducing exploration to a minimum.

Surgical Results: Our own work has not yet led to employment of these technics in the treatment of patients suffering from coronary arteriosclerosis, but there are reported successes with the direct approach. As early as 1953, Murray reported successful excision of occluding segments of coronary arteries with homograft replacement.

More recently, Bailey and co-workers[11] reported two successful endarterectomies and have done several more in humans. Bailey has, after his two reported cases, resorted to the use of cardiac bypass, aortotomy, and retrograde curretting of the obstruction to attain restoration of vascular lumen. Evaluation of results cannot yet be made.

This same clinic reports 10 patients subjected to coronary endarterectomy without mortality. With followup of one year or less, nine patients are without symptoms, and one is moderately improved. Postoperative coronary arteriography is planned, but has not been done.

Summary

In summary, experimental investigation indicates that direct relief of obstructive coronary atherosclerosis may be possible. Successful cases have been reported. Criteria for selection of those patients suitable for further attempts are not established. X-ray visualization of the coronary arterial tree will help select candidates for this type of surgery. The direct attack may be coronary thromboendarterectomy, or the employment of arterial bypass to restore blood flow. Serious, cautious, and critical investigation can lead to evaluation of this method of treatment.

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Clinical Studies

Electrocardiographic Effects of Eyeball Compression*

LEO SCHAMROTH, M.B., M.R.C.P.E.

Johannesburg, South Africa

"A physical sign or method for lack of better, may serve the purpose of the moment, it serves no purpose in the pursuit of science till the measure of its fallibility is taken."

THOMAS LEWIS

THE ROLE of the nervous system in the cardiac arrhythmias is a complex one and has not as yet been completely elucidated. Its action is mediated chiefly via the vagus nerve and to a lesser extent the cardiac sympathetic nerves. A wealth of data has accumulated about vagal action in animal experimentation but by comparison there is a relative paucity of similar observation in man. This study is an attempt to evaluate electrocardiographically the role of vagal action in cardiac rhythm by means of eyeball compression (Aschner-Dagnini reflex), and to correlate the results with those of laboratory investigation.

METHODS AND MATERIALS

One hundred forty-eight African subjects were investigated. These were grouped into the following test categories: (1) One hundred and two patients with cardiac disease (congenital, subacute and chronic rheumatic, hypertensive, pulmonary and cryptogenic); (2) Eighteen patients with noncardiac disease (pneumonia, epilepsy, tuberculosis, rheumatoid arthritis, anemia and malnutrition); (3) Twenty-eight healthy African nurses as normal controls. The cardiac patients were further subdivided: (a) those with sinus rhythm and receiving digitalis; (b) those with sinus rhythm and not receiving digitalis; (c) those with auricular fibrillation and receiving digitalis.

The ventricular rates ranged from 60 to 130 beats per minute. Compression was performed for periods of 3 to 20 seconds by manual pressure simultaneously on both eyes sufficiently firm to cause slight pain. This maneuver was repeated several times during each recording and the effect of carotid sinus pressure was also noted. All patients with a history of eye disease were excluded. A direct recording electrocardiograph was used necessitating retouching of the faint QRS complexes of Figures 2–6, 8 and 10.

RESULTS

The following effects were noted (illustrative electrocardiograms are shown in Figures 1 to 11):

(1) Sinus depression.

(2) Shift in the site of the primary pacemaker.

(3) Auriculoventricular dissociation.

(4) Precipitation of ventricular ectopic beats with fixed coupling.

(5) Abolition of coupled ventricular ectopic beats.

(6) Transient lengthening of the coupling interval with intermittent parasystole.

(7) Variations in the duration of the P-R intervals.

(8) Prolonged P-R intervals and higher degrees of auriculoventricular block.

(9) Transient auricular and ventricular tachycardia.

* From the Baragwanath Hospital and University of the Witwatersrand, Johannesburg.

TABLE I

Electrocardiographic Effects of Eyeball Compression

Test groups	Number of cases tested	Sinus depression	Shift of the primary pacemaker	Auriculo-ventricular dissociation	Precipitation of ectopic beats	No change	Number of cases tested	Abolition of ectopic beats
(1) Cardiac disease								
(a) With sinus rhythm and receiving digitalis	30	28 (93.3)	25 (83.3)	14 (46.6)	17 (56.6)	2 (6.6)	10	3 (30)
(b) With sinus rhythm and *not* receiving digitalis	40	37 (92.5)	26 (65.0)	8 (20.0)	4 (10.0)	3 (7.5)	10	0 (0)
(c) With auricular fibrillation and receiving digitalis	12	3* (25)	—	—	—	9 (75)		
(2) Disease other than cardiac	18	18 (100)	14 (77.7)	4 (22.2)	2 (11.1)	0 (0)		
(3) Normal controls	28	28 (100)	18 (64.3)	2 (7.1)	1 (3.6)	0 (0)		

* A–V depression. ( ) percentage.

(10) Nodal and ventricular escape.

(11) No change.

The first four of these listed effects were those most frequently encountered. Their incidence is illustrated in Table I.

(1) *Sinus Depression:* This was a frequent finding and occurred in 95.7 per cent of cases with sinus rhythm (e.g., Figures 1–8, 10, 11). There was no significant discrepancy between the test groups. The depression varied from sinus bradycardia with accentuated sinus arrhythmia to sinoauricular block with periods of standstill lasting up to 4 seconds. The latter was followed by either a shift in the site of the primary pacemaker with a conducted beat, nodal or ventricular escape, or auriculoventricular dissociation. It is of interest to note that 5 of the 28 normal controls showed hypersensitive reactions to eyeball compression by the exhibition of periods of sinus standstill lasting up to 4 seconds.

(2) *Shift of the Primary Pacemaker:* Fluctuations in the size and shape of the P wave were readily induced in 71.5 per cent of cases with sinus rhythm (Fig. 1, 2, 4, 6, 7, 11). There was no marked discrepancy between the test groups.

(3) *Auriculoventricular Dissociation:* This change was noted in 25 per cent of cases with initial sinus rhythm, but significantly less frequent in the normal controls (7.1 per cent) than the other test groups (Table I). The highest incidence (46.6 per cent) was found in those patients receiving digitalis. The abnormality persisted for periods ranging from a few seconds (Fig. 1) to one minute (Fig. 3–6). Transient "bursts" of tachycardia of the subsidiary pacemaker were noted in three instances (Fig. 3 and 5).

(4) *Precipitation of Ventricular Ectopic Beats with Fixed Coupling:* The incidence of this phenomenon demonstrated the most significant difference between the test groups. The highest

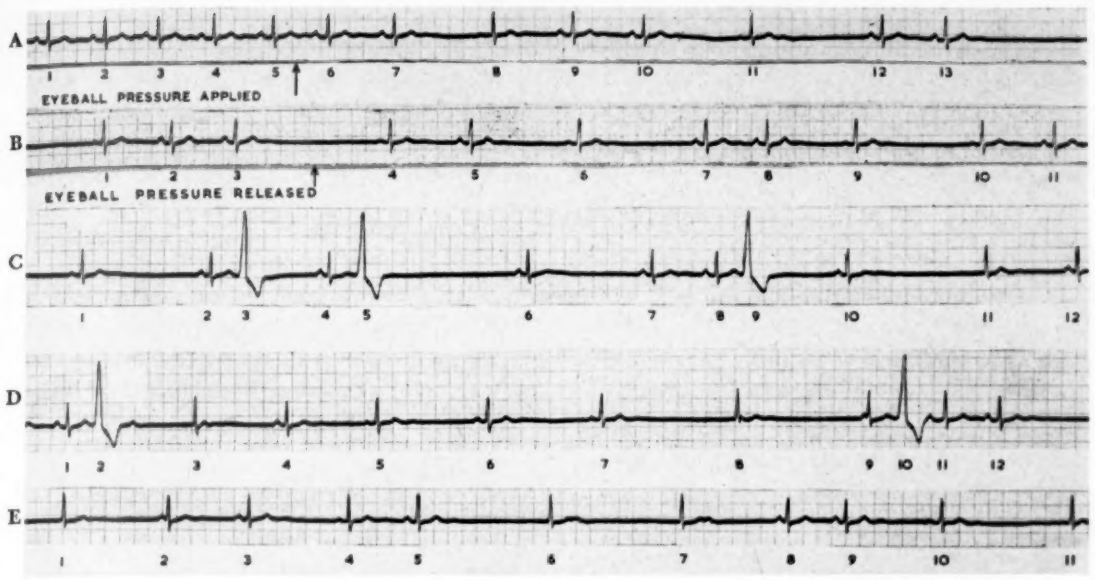

Fig. 1. Electrocardiogram, standard lead 2 (continuous strip), of a 26-year-old female with grand mal epilepsy and receiving phenytoin. This shows a basic sinus rhythm with R-R intervals of 0.8 sec and P-R intervals of 0.2 sec (complexes A 1 to 6). One second after the application of eyeball compression (row A) there is sinus bradycardia with a general pattern of marked sinus arrhythmia. A change in the shape of the P wave (shift in the site of the primary pacemaker) is noted in complex A 8, and this form of P wave occurs sporadically hereafter (A 11; B 1, 4, 6, 9, and 10; C 1; D 5, 6, and 7; E 4 and 10). Dissociated beats are seen in complexes C 11; D 3, 8, and 9; E 1, 2, 6, 7, and 11, with the subsidiary pacemaker in these instances located in the A–V node. The P-R intervals of the conducted beats vary. Occasional ventricular ectopic beats are seen which are accurately coupled (0.40 sec) to the preceding sinus beats viz., C 2, 4, and 8; D 1, and to one dissociated beat viz., D 9. The P wave following the ectopic beat D 2 is blocked. The P-R interval of complex D 11 is prolonged (0.26 sec). This arrhythmia persisted for a further minute followed by a return to the basic sinus rhythm.

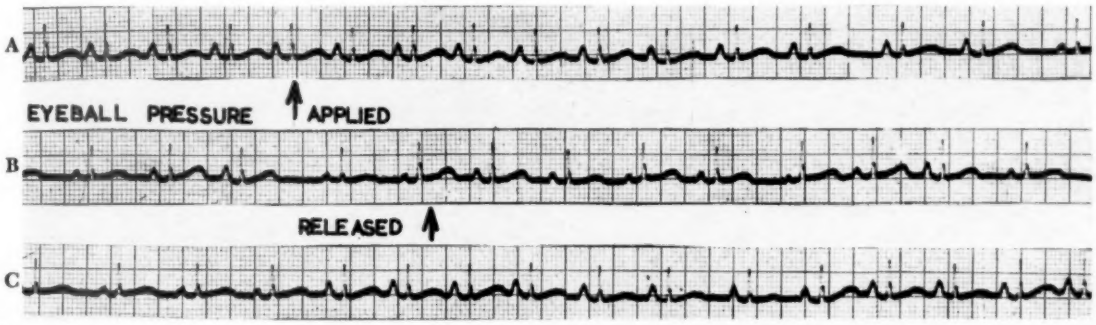

Fig. 2. Electrocardiogram, standard lead 2 (continuous strip), of a five-year-old male with tetralogy of Fallot and not on digitalis therapy. This shows sinus bradycardia, sinus arrhythmia, and variation in the size and shape of the P wave following eyeball compression.

incidence occurred in those patients with heart disease and receiving digitalis, 56.6 per cent, compared with 10 per cent and 11.1 per cent in the other disease groups and only 3.6 per cent (1 in 28) of the normal controls (Table I). Furthermore, in the group receiving digitalis the tendency was for coupled beats to be precipitated in "runs" which often persisted for several minutes (Fig. 7). This contrasted with the other test groups where sporadic coupling was the most frequent finding (Fig. 1).

(5) *Abolition of Coupled Ventricular Ectopic Beats:* This effect occurred in 30 per cent (three out of ten) of cases with cardiac disease and receiving digitalis (Fig. 9–11). It was also noted after the precipitation of coupled ectopic beats following sinus rhythm and the re-application of eyeball compression (Fig. 8). The sinus rhythm

so effected was maintained for periods of 12 to 109 seconds with ultimate return to the basic bigeminal rhythm. In one case (Fig. 9), the second application of eyeball compression effected a disappearance of the bigeminal rhythm for a followup period of five weeks. No change occurred in 10 cases of cardiac disease with bigeminal rhythm and not receiving digitalis.

(6) *Transient Lengthening of the Coupling Interval with Intermittent Parasystole:* This was observed in two instances (Fig. 10, 11), both of which were probable examples of intermittent parasystole (Langendorf and Pick[1]), viz., a parasystolic focus activated by a coupled ectopic beat.

(7) *Variations in the Duration of the P-R Intervals;* (8) *Prolonged P-R Intervals and Higher Degrees of Auriculoventricular Block:* These were not infrequently observed and occurred sporadically. There was no appreciable statistical difference in the incidence of these arrhythmias between the disease test groups; it was however uncommon in the normal controls.

(9) *Transient Auricular and Ventricular Tachycardia:* This was most often observed during periods of auriculoventricular dissociation (Fig. 3, 5), and occasionally as a "rebound" following precipitation of coupled ectopic beats (Fig. 8).

(10) *Nodal and Ventricular Escape:* This

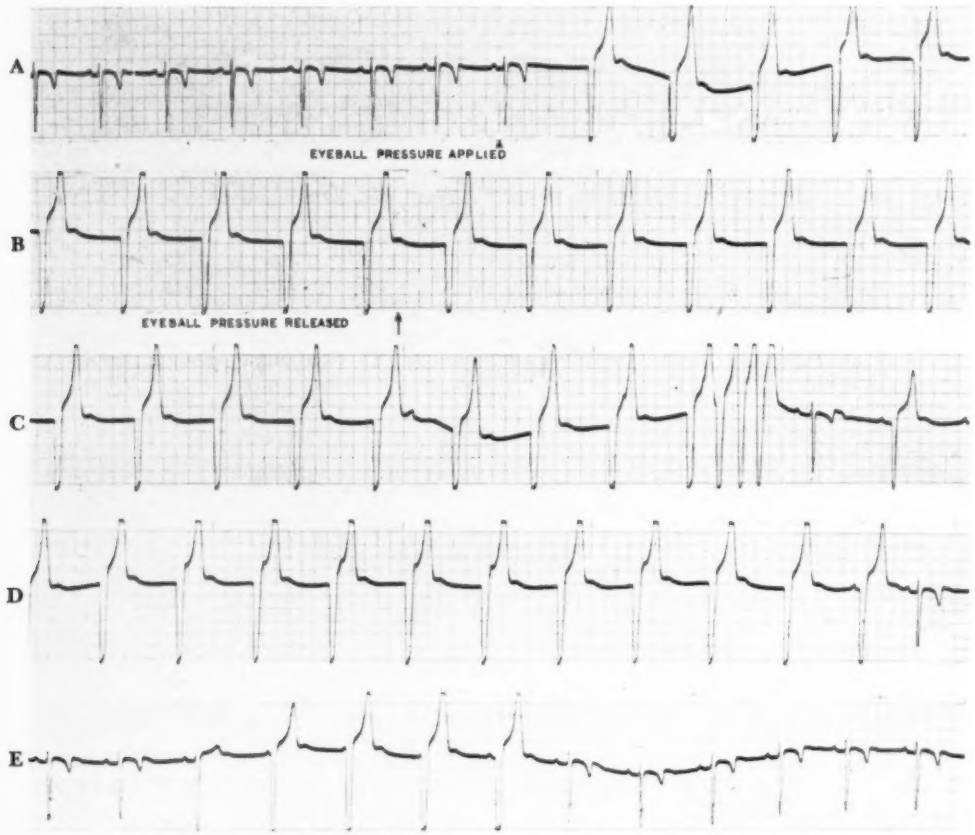

Fig. 3. Electrocardiogram, lead V_1 (continuous strip), of a 30-year-old male with a ventricular septal defect and partially digitalized. This shows a basic sinus rhythm with R-R intervals of 1.0 to 1.8 sec, and P-R intervals of 0.2 sec (the first eight complexes in row A). One sec after the application of eyeball compression there is auriculoventricular dissociation with the subsidiary pacemaker discharging at a rate of 1.28 sec (row A). A short "burst" of paroxysmal ventricular tachycardia is noted in row C. This is followed by a ventricular capture by a sinus impulse with a prolonged P-R interval of 0.26 sec. The next complex represents a fusion beat. Sinus rhythm is again seen in the last complex of row D and the first two complexes in row E. This is followed by two fusion beats, a period of auriculoventricular dissociation and ultimate sinus rhythm which persisted. The total period of abnormality was 59 sec. Similar graphs were obtained on three other attempts at eyeball compression during the following 30 minutes and could easily be induced on other occasions.

usually followed prolonged periods of sinus standstill as was well demonstrated in those normal controls with hypersensitive reactions.

(11) *No Change:* No effect from eyeball compression was observed in five cases with a basic sinus rhythm (Table I). Of these, two had the pattern of right bundle branch block, one had the pattern of complete heart block, and the remaining two had sinus tachycardia with rates of 130 per minute. Minimal slowing of the ventricular rate occurred in three of the twelve cases with auricular fibrillation and the remaining nine showed no change.

Variability of the Effects: A combination of effects mentioned under 1 to 10 was frequently found in the same record (Fig. 1).

The interval from the commencement of eyeball compression to the time of onset of changes ranged from 1 to 23 seconds. The duration of the changes so effected varied from a few seconds to 15 minutes with ultimate return (in nearly all cases) to the original rhythm. A repetition of changes could in most instances be effected at the same recording by the re-application of eyeball compression.

The effect of one application sometimes resulted in irregular periods of fluctuating changes probably corresponding to fluctuating intensities of vagal effect (Fig. 1, 3, 5, and 8).

The precipitation of subsidiary pacemaker activity, e.g., ectopic beats and auriculoventricular dissociation, nearly always followed a bradycardic effect. This confirms the observation by Langendorf *et al.*[2] that coupled ectopic beats tend to follow the longer ventricular cycles—the "rule of bigeminy."

No ocular complications occurred in any of the subjects.

Comparison with Carotid Sinus Compression: In comparison with eyeball compression, carotid sinus compression was relatively ineffectual, causing changes in only 15 per cent of cases. These consisted of minimal sinus bradycardia and occasional shift of the primary pacemaker. None of the other effects listed above were observed. This difference in effect between eyeball compression and carotid sinus compression was noted 40 years ago (Levine[3]) but has apparently not been stressed since.

Discussion

Effects of Vagal Stimulation: The afferent arc of the oculocardiac reflex is the trigeminal nerve which when stimulated by eyeball compression causes an increase in vagal tone. The latter exerts a restraining action on the heart which is well demonstrated in this study by the varying degrees of sinus depression in all test groups. This may be followed by a return to normal rhythm, momentary nodal or ventricular escape, or subsidiary ectopic activity, e.g., coupled ectopic beats or auriculoventricular dissociation. The depressive effect is most marked on the upper regions of the sino-auricular node causing, in the majority of cases, frequent shifts in the site of the primary pacemaker to the lower regions of the node or auricle.

The precipitation of ectopic rhythms was most frequently associated with the administration of digitalis which is known to cause a biochemical change in the myocardium. Ectopic activity was much less evident in those patients not receiving digitalis where the percentage of positive reactions could be accounted for by the concomitant toxemic, infective, or anoxic processes. In the normal controls, these arrhythmias were exceedingly rare and occurred as a few sporadic coupled beats in only one of the 28 in that test group.

Previous reports of precipitation of coupled ectopic beats by means of eyeball compression[4–7] and carotid sinus compression [8–11] were likewise usually associated with complex cardiac conditions. These patients had either been receiving drugs (most commonly digitalis) or the ectopic beats had been observed on previous occasions and were thus "reactivated" or precipitated by these manoeuvers.

Importance of Myocardial Abnormality and Digitalis: It would thus appear that vagal stimulation alone rarely produces ectopic rhythms, but that an abnormal myocardial focus is necessary before this phenomenon can occur. This is supported by the hypersensitive reactions seen in five of the normal control cases; in these persons vagal stimulation caused marked bradycardic effects but no ectopic rhythms. Similarly, in a subject with a normal heart and showing intense vagal activity (Chesler and Schamroth[12]) the

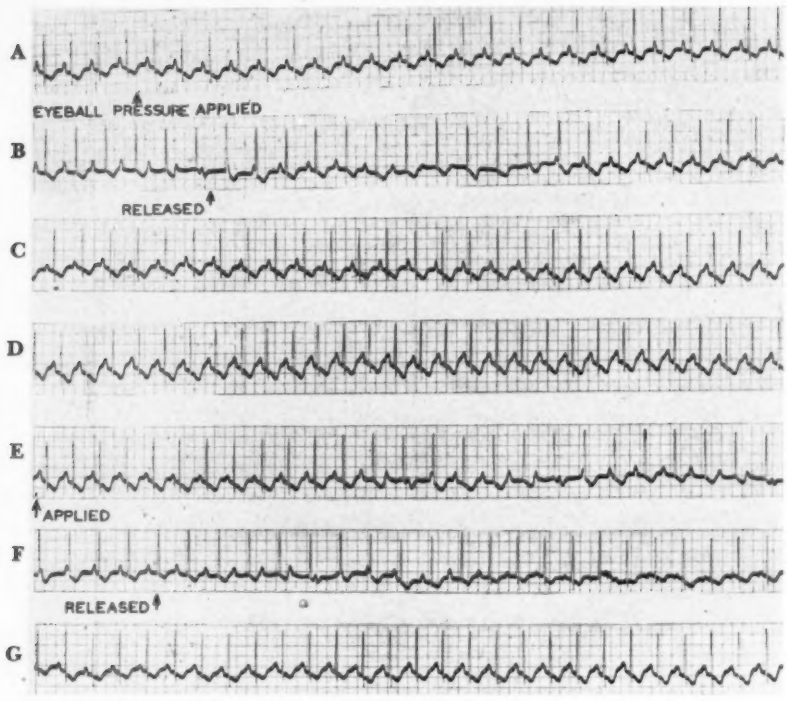

Fig. 4. Electrocardiogram, standard lead 2 (continuous strip), of a 28-year-old female with mitral stenosis and incompetence and fully digitalized. This shows a basic sinus rhythm with R-R intervals of 0.56 sec (row A). Auriculoventricular dissociation commences 14 sec after the application of eyeball compression (row B) and persists for 9 seconds. This is followed by sinus rhythm (end of row B, and rows C and D). The re-application of eyeball compression (row E) is followed by another period of auriculoventricular dissociation which commences 6 sec later and persists for 15 sec (rows E and F). This is followed by a period of nodal rhythm (row F) and final return to sinus rhythm.

only electrocardiographic effects were varying degrees of sino-auricular and auriculoventricular block with not a single instance of ectopic activity.

These clinical findings are in accord with those of animal experiments where vagal stimulation *alone* rarely provokes ectopic rhythms. Here too, complex conditions must exist which will predispose or "condition" the heart before vagal stimulation will elicit ectopic rhythms. Thus, in the experimental animal, vagal stimulation has resulted in the exhibition of coupled ectopic beats when combined with the administration of thiobarbiturates,[13] digitalis,[14] and aconitine.[15] The latter is the only known experimental method whereby bigeminal rhythm due to fixed coupling of ventricular ectopic beats can be produced with any degree of certainty.

Other ectopic arrhythmias such as paroxysmal ventricular tachycardia, A–V nodal rhythm, and auricular arrhythmias may also be precipitated clinically and experimentally by vagal stimulation.[16–20]

Mechanism of Coupled Ventricular Ectopic Beats: The fixed coupling of a ventricular ectopic beat to the preceding sinus beat suggests that the ectopic beat is in some way dependent on or precipitated by the sinus beat. The mechanism of this phenomenon is still debatable and at present two theories are current. The re-entry theory postulates a circus movement viz., the re-entry of the original impulse of the initiating impulse into an altered or partially refractory area by a circuitous route with consequent delayed depolarization. While it is highly probable that under certain circumstances the re-entry mechanism is operative, e.g., return extrasystoles, its application to the fixed coupling of ectopic beats is open to question (for detailed discussion see Scherf and Schott[11]). The other theory postulates

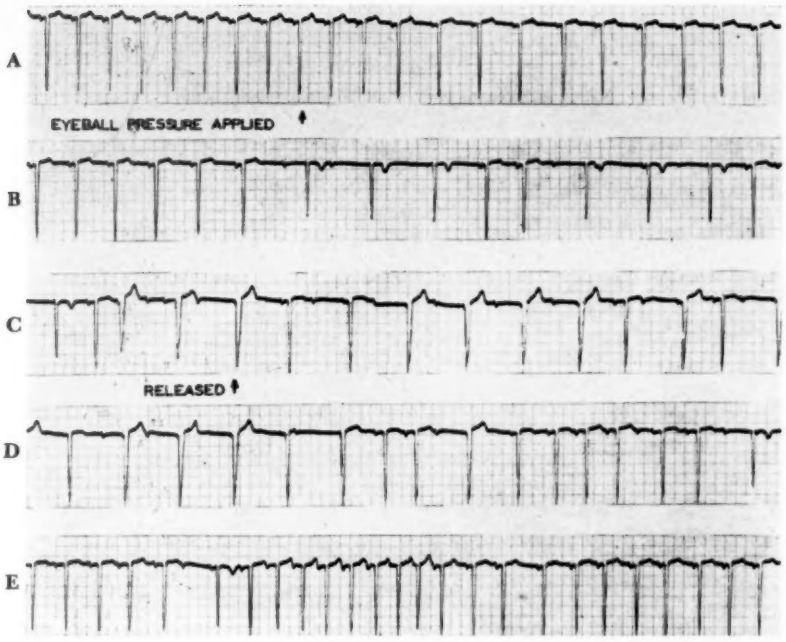

Fig. 5. Electrocardiogram, lead V_2 (continuous strip), of a 30-year-old male with mitral stenosis and incompetence and partially digitalized. This shows sinus bradycardia which commences one sec after the application of eyeball compression (row A). Auriculoventricular dissociation commences in row B with a lower nodal subsidiary pacemaker (row B, 7th, 8th, and 9th complexes) and terminates toward the end of row E. This period of auriculoventricular dissociation also includes varying "high" ventricular subsidiary pacemakers (row C, 4th, 5th, 7th, 8th, 9th, 10th, and 12th complexes); ventricular captures (row B, 10th and 11th complexes), a "burst" of ventricular tachycardia (middle of row E), and a coupled ectopic beat (row C, 3rd complex). Auricular tachycardia is seen in rows C, D, and E.

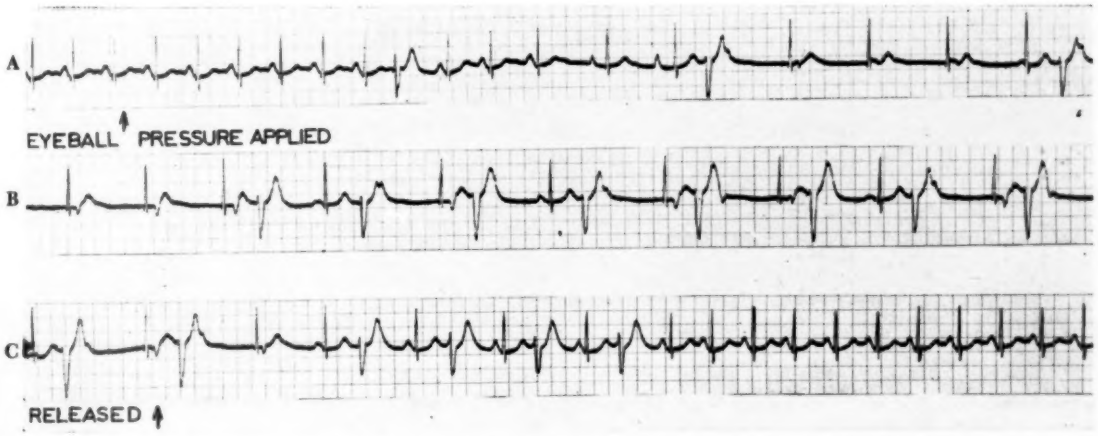

Fig. 6. Electrocardiogram, standard lead 2 (continuous strip), of a 31-year-old female with mitral stenosis and fully digitalized. This shows sinus bradycardia, shift of the primary pacemaker, auriculoventricular dissociation and precipitation of coupled ectopic beats following eyeball compression.

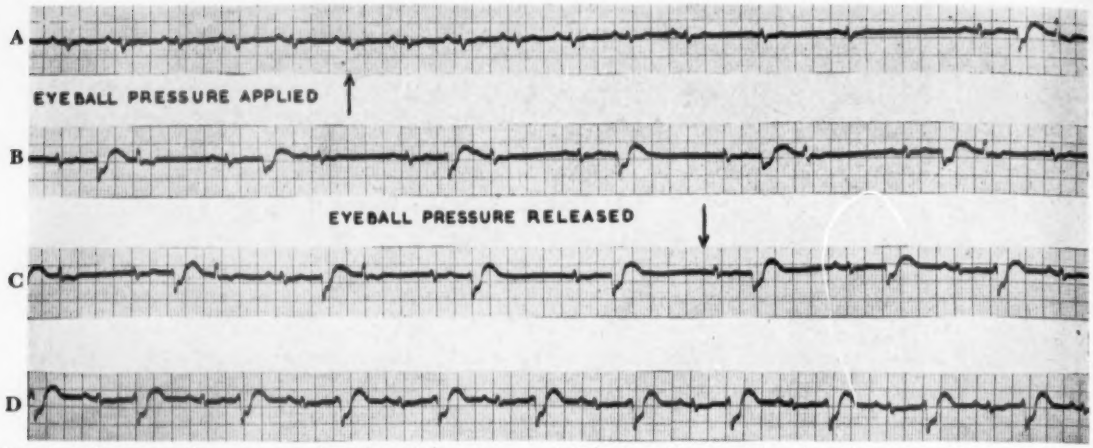

Fig. 7. Electrocardiogram, standard lead 2 (continuous strip), of a 26-year-old male with transposition of the great vessels; in congestive cardiac failure and fully digitalized. This shows sinus bradycardia, shift of the primary pacemaker and interpolated ectopic beats following eyeball compression. The arrhythmia persisted for 15 minutes.

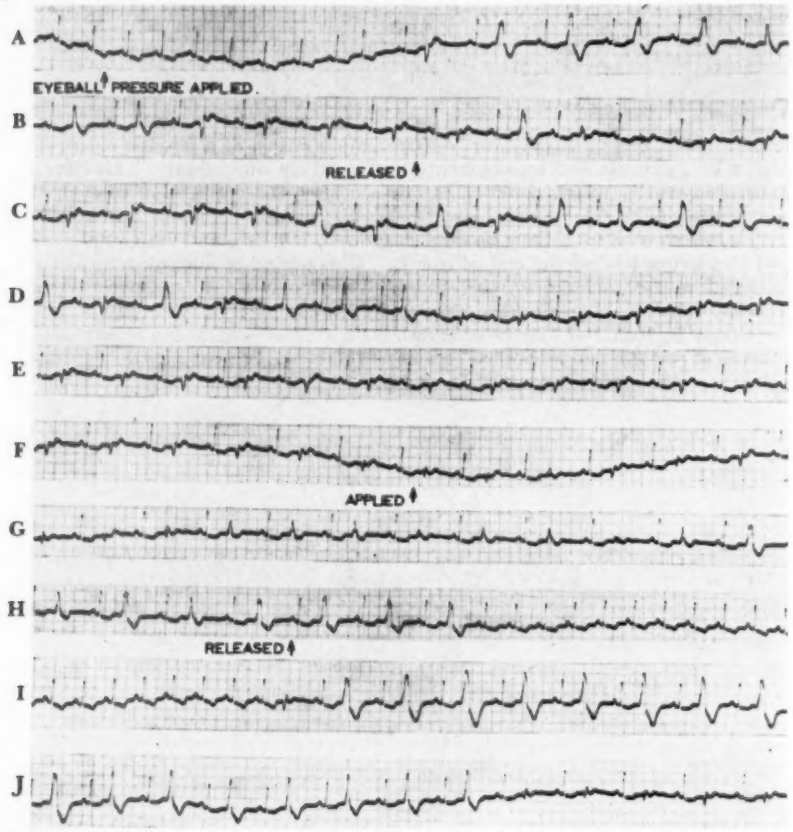

Fig. 8. Electrocardiogram, standard lead 2 (continuous strip), of a 42-year-old female with hypertensive cardiac failure and receiving digitalis and reserpine. This shows a basic sinus rhythm with respiratory sinus arrhythmia and average R-R intervals of 0.68 sec (row A, first 11 complexes). Coupled ectopic beats commence 6 sec after the application of eyeball compression, following the longest R-R interval in row A (0.84 sec). The ectopic beats arise from varying foci each with fixed coupling to the preceding sinus beat. The ectopic foci tend to become stabilized around one focus during a period as reflected in the latter half of row D, and rows E and F. The reapplication of eyeball compression (row F) may have been instrumental in once again initiating fluctuations in the location of the ectopic foci (rows G and H). Sinus tachycardia (R-R intervals of 0.56 sec) is seen in the latter half of row H and the beginning of row I. This reverts back to coupled rhythm (rows I and J) which persisted for 24 hours until concomitant with reduction in the dosage of digitalis, a return to normal sinus rhythm occurred.

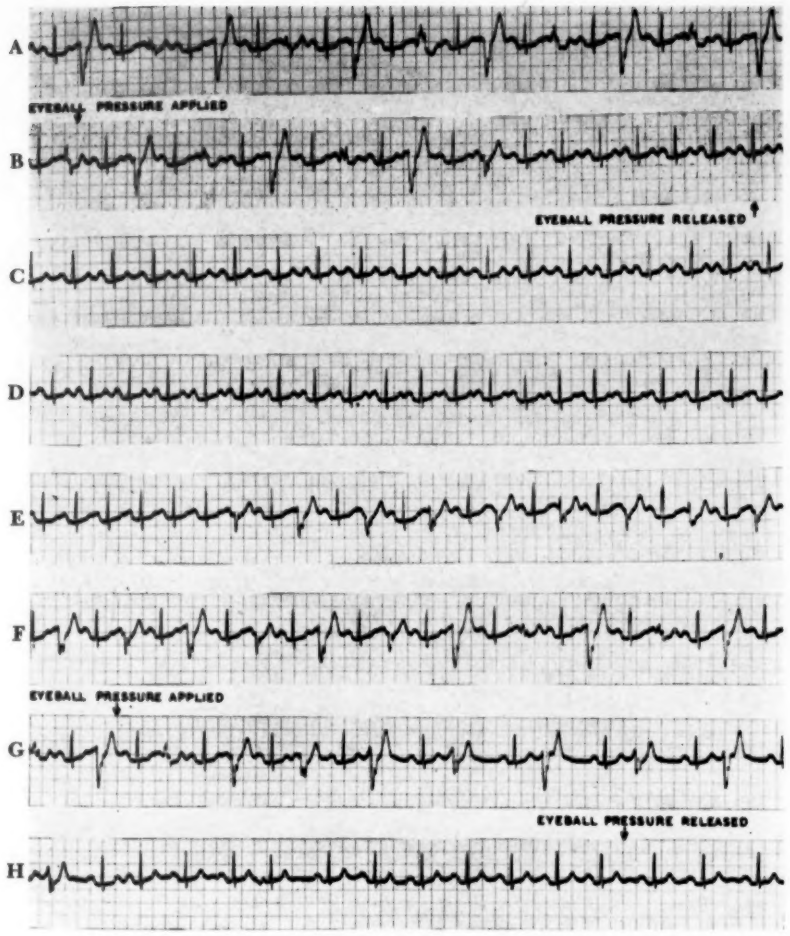

Fig. 9. Electrocardiogram, standard lead 2 (continuous strip), of a 22-year-old male with mitral stenosis and fully digitalized. This shows a basic bigeminal rhythm (row A) with accurately coupled ectopic beats arising from different foci alternately (coupling intervals of 0.44 and 0.46 sec). The P wave has the configuration of a P "mitrale." The P-R intervals are 0.22 sec and the P-P intervals 0.56 sec in duration. The R-R intervals of the sinus beats are 1.08 sec. Normal sinus rhythm with P-P intervals of 0.56 sec follows 6 sec after the application of eyeball compression (row B) and persists for 31 sec (rows B, C, D, and E). This is followed by a return to bigeminal rhythm which develops into a similar pattern to that found in row A (rows E, F, and G). The re-application of eyeball compression (row G) is followed 11.6 sec later by sinus bradycardia and normal sinus rhythm (row H) which now persisted for a follow-up period of five weeks. An auricular ectopic beat is noted in row H—6th complex.

that the ectopic impulse is due to an after-discharge in a circumscribed area which has been altered physically or chemically.[21,22] This after-discharge is due to a local increase in negative after-potential following the initiating beat. When this negative potential reaches a critical level, depolarization occurs and a propagated impulse follows. Thus the area is depolarized twice in rapid succession.

This phenomenon may be explained on the basis of the Wedensky effect and/or Wedensky facilitation. Wedensky[23] in 1886 observed that a subthreshold stimulus to a sciatic-gastrocnemius preparation of a frog did not (as anticipated) elicit a contraction. The same subthreshold stimulus, however, when applied *after* the application of a maximal induction shock now initiated a tetanus. This demonstrates a tempo-

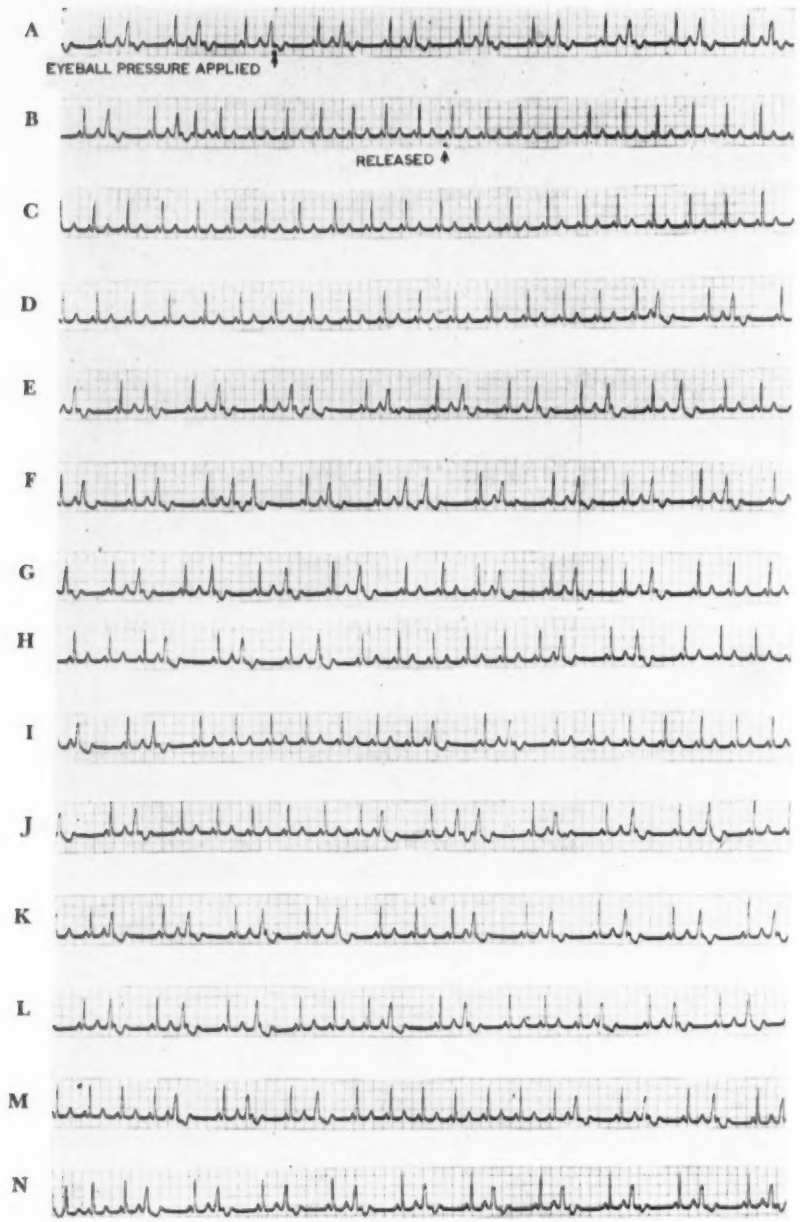

Fig. 10. Electrocardiogram, standard lead 2 (continuous strip), of a 36-year-old male with cryptogenic cardiac failure of the type seen in the African. There was no history of drug ingestion but the possibility of "drug" administration by a witch-doctor was suspected. This shows a basic bigeminal rhythm with fixed coupling of ventricular ectopic beats (0.5 sec). The R-R intervals of the sinus beats are 1.46 sec (row A). The ectopic beats are abolished 19.4 sec after the application of eyeball compression and normal sinus rhythm is established. This sinus rhythm is initiated with a nodal beat. The R-R intervals of the sinus rhythm are 0.7 sec in duration (row B). This rhythm persists for 109 sec with gradual lengthening of the cycle length (rows B, C, and D). The double cycle length (2 × R-R interval) at the commencement of this sinus rhythm is 1.24 sec in duration. This is less than the intersinus cycle length of 1.46 sec in row A. The double cycle length at the end of the period of sinus rhythm and before the recommencement of coupled rhythm is 1.5 sec and thus approximates the intersinus cycle length of row A. The R-R interval before the recommencement of coupled rhythm is the longest (0.76 sec). The initial coupling interval in row D is 0.4 sec and consecutive coupling intervals thereafter are 0.44 sec (row D), and 0.48 sec, 0.48 sec, 0.48 sec, 0.48 sec (row E). This is followed by a paired ectopic beat with an ectopic cycle length of 0.44 second. The interectopic cycle lengths of this series are 1.52, 1.52, 1.48, 1.48 and 1.48 sec, respectively.

rary increase in excitability following the maximal induction shock. The Wedensky effect was observed in the Purkinje fibers of the dog by Goldenberg and Rothberger[24] and their investigations showed that this effect could be invoked in the mechanism of coupled ectopic beats. The initiating or precipitating impulse is likened to the maximal induction shock and following the temporary increase in excitability consequent upon this shock, an ectopic impulse is propagated from a center whose activity is normally subthreshold.

Wedensky[25] (1903) also discovered that when a nerve impulse reaches a partially or completely blocked zone, the excitability *beyond* the block is enhanced. This phenomenon is known as Wedensky facilitation.

These aforementioned principles may possibly elucidate the role of the vagus in the mechanism of coupled ectopic beats. Thus, the presence of subthreshold activity in a chemically or structurally abnormal myocardial focus satisfies the conditions for the precipitation of coupled ectopic beats by the Wedensky effect. This effect may now be enhanced or precipitated by vagal stimulation which by virtue of its blocking action on the sino-auricular and auriculoventricular nodes, increases the excitability beyond the block by the mechanism of Wedensky facilitation.

The frequency of coupled ectopic beats with digitalis intoxication may thus be readily understood when it is appreciated that digitalis causes both a vagotonic effect and a local metabolic change in cardiac muscle. Furthermore, the tendency for sporadic and prolonged periods of coupling to follow the longer ventricular cycles —the "rule of bigeminy" could be explained by a momentary increase in vagal tone as revealed by the temporary bradycardia.

It could be further postulated that the excitability of the subsidiary focus may be so enhanced as to assume and perpetuate its own inherent rhythmicity, manifesting as auriculoventricular dissociation, ventricular tachycardia, or intermittent parasystole.

Mechanism of Suppression of Ventricular Ectopic Beats: Suppression of ventricular ectopic beats has been observed following carotid sinus compression.[26–29] This has been attributed to incidental pressure on the sympathetic pressor-receptor nerves during this maneuver, with a consequent decrease in sympathetic tone. The paradoxic effects of precipitation and abolition of ectopic beats by carotid sinus compression have also been thought to be dependent on the condition of the heart and particularly its rhythm when stimulation is applied.[11]

The mechanism of suppression of ectopic beats following eyeball compression is not clear. Several possibilities suggest themselves, viz.: (1) The abolition may be due to a rebound phenomenon, i.e., the fluctuating vagal effect elicited by eyeball compression may result in temporary diminution of vagal tone concomitant with an increase in sinus rate and diminution in Wedensky facilitation. Thus in three cases of the above series where this phenomenon was noted,

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(Fig. 10—continued.) The intersinus cycle length is 1.46 seconds. It is thus evident that the increase in coupling intervals is due to a discrepancy between the intersinus and interectopic intervals.

The paired ectopic beats (row E) are followed by a pause and then a coupled ectopic beat with a coupling interval of 0.4 second. Subsequent coupled ectopic beats show a gradual increase in the coupling intervals which is again due to a discrepancy between the intersinus and interectopic lengths (1.46 and 1.52 sec, respectively). This particular series terminates with 2 sinus beats (row E).

This pattern is repeated sporadically hereafter (Rows F to N) with the first coupling interval always fixed at 0.4 second. This arrhythmia finally terminates in row N with a change to the initial bigeminal rhythm of coupled ectopic beats with fixed coupling.

Comment: In the pattern of intermittent coupling (rows E to N), the occurrence of interectopic intervals of fixed duration indicates a simple parasystole with discharge rate slower than that of the dominant pacemaker. The parasystole is always initiated by a coupled ectopic beat with a fixed coupling interval. The longer interectopic intervals bridging an intermittence of the bigeminy in this pattern is shorter than a multiple of the fixed interectopic intervals of 1.5 seconds. This suggests an intermittence of the parasystole (cf. Langendorf and Pick[1]).

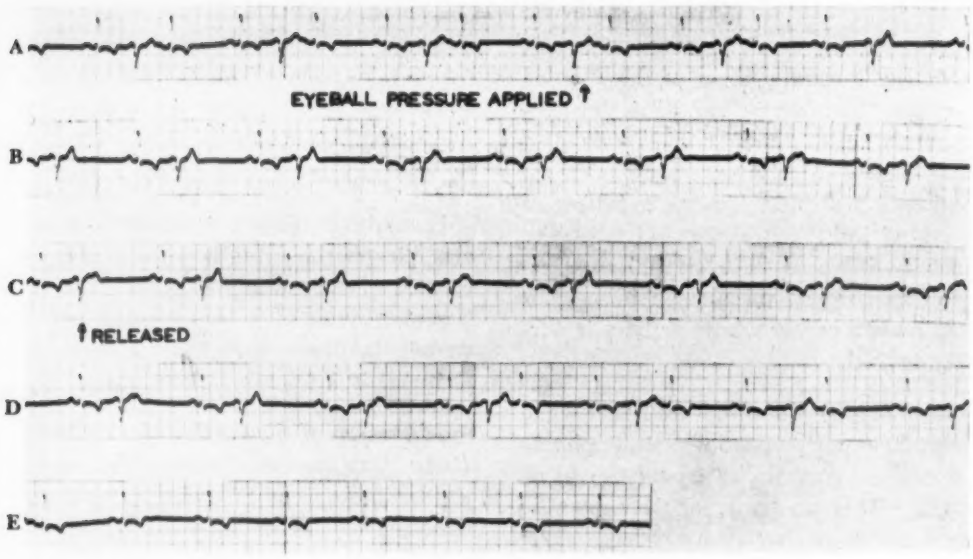

Fig. 11. Electrocardiogram, standard lead 2 (continuous strip), of a 37-year-old male with hypertension, congestive cardiac failure, fully digitalized and on reserpine therapy. This shows a basic sinus rhythm with interpolated ectopic beats accurately coupled at 0.60 sec (row A). The interectopic intervals of row A measure 11.3, 11.3, 11.32, 11.32 and 11.38 sec, respectively. Four sec after the application of eyeball compression, there is lengthening of the coupling interval to 0.72 sec (last coupled beat in row A). This results in the abolition of the immediate postectopic beat as this now occurs during the refractory period of the ectopic beat. This is followed by coupled beats with fixed coupling of 0.60 sec (rows B, C, and the first 4 complexes in row D). The last 4 coupled beats in row D show a progressive increase in the coupling intervals viz., 0.60, 0.66, 0.74, and 0.74 sec, respectively. Following this there is abolition of the ectopic beats and the establishment of normal sinus rhythm which persisted for 25 sec and was then followed by a return to the basic bigeminal rhythm. The increasing coupling intervals associated with increasing interectopic intervals suggest a form of intermittent parasystole with a Wenckebach type of disturbance in the parasystolic focus (cf. Fig. 10). The transient increase in the coupling interval in row A may be due to the same mechanism.

the suppression of ectopic beats did not follow immediately on eyeball compression, but after relatively long intervals when a rebound could conceivably have occurred (Fig. 10, 19 sec; Fig. 8, 27 sec; Fig. 11, 51 sec). (2) An increased sinus rate may discharge the ectopic impulse prematurely (Fig. 8 and 10). (3) An increase in the coupling interval may facilitate the premature discharge of the ectopic impulse by the now relatively fast sinus impulses. (4) Vagal tone may affect the depolarization and repolarization of the ectopic focus directly; this however seems unlikely.

Stimulation of the sympathetic nervous system by eyeball compression appears unlikely, and it seems that the basic mechanism for the suppression of ectopic beats by this method is probably a fluctuation in vagal tone with the exact consequential *modus operandi* still obscure.

The function of the vagus nerve as an inhibitory force in cardiac action is a well-documented and accepted physiologic concept. This study emphasizes the role of the vagus in the vagaries of the ectopic arrhythmias; and it may well be that future studies may prove this role to be more important than has hitherto been anticipated.

Summary

The electrocardiographic effects of eyeball compression were studied in 148 subjects comprising (1) 102 patients with cardiac disease; (2) 18 patients with noncardiac disease; (3) 28 nurses as normal controls.

The principal changes elicited by this maneuver were a general depressive effect on cardiac rhythm and the precipitation of ectopic rhythms (coupled ectopic beats, A–V dissocia-

tion, auricular and ventricular tachycardia, and intermittent parasystole).

The incidence of the precipitation of ectopic rhythms was significantly greater in those patients receiving digitalis.

The possible role of vagal action in the ectopic arrhythmias is discussed.

Acknowledgments

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Induced Respiratory and Circulatory Changes in Unilateral Disequilibrium*

LIPMAN HALPERN, M.D., KARL BRAUN, M.D., F.A.C.C., *and* MARCEL ELIAKIM, M.D.

Jerusalem, Israel

UNILATERAL disequilibrium is manifested by the displacement of the body and the homolateral extremities to the affected side. It may be a part of certain diseases of the nervous system such as multiple sclerosis, or it may appear without other neurological manifestations. In some patients suffering from unilateral disequilibrium, unilateral sensory disturbances have been noted. The sensory disturbances were found to be induced by the abnormal postural pattern.[1–6] They are phenomenologically and physiologically of a special nature, occurring in spite of the anatomical integrity of the sense organs and appearing on that side of the body which corresponds to the side of the disequilibrium.[7] The induced sensory disturbances manifest themselves by displacement of the horizontal and vertical coordinates in the visual, tactile, and heptic spheres, as well as by qualitative and quantitative alterations of perception. A most impressive and characteristic feature observed in patients suffering from the disturbances mentioned above, is the mutual influence of motor and sensory functions. Thus, motor stimuli, such as changing the head posture, or sensory stimuli, such as the closure of both eyes, the alternate opening of each eye or the application of coloured filters to either eye, improve or deteriorate the equilibrium and the induced sensory disturbances.[3–8] The fact that sensory disturbances can be dramatically induced by unilateral disequilibrium is the basis of the sensorimotor induction syndrome.

The following study was stimulated by the clinical observation that the conditions which influenced adversely the disequilibrium of patients with the sensorimotor induction syndrome frequently caused palpitation, hyperpnea, nausea and/or a change of skin colour. The following investigations were therefore carried out in order to determine whether the experimental conditions which were found to influence the motor and sensory functions also affect the functions of respiration and circulation.

SUBJECTS AND METHODS

Three patients manifesting the features of the sensorimotor induction syndrome in unilateral disequilibrium were examined. The syndrome was left sided in two patients and right sided in the third. Respiration, pulse rate, blood pressure and electrocardiograms were recorded in all patients. A chest pneumograph was used for recording the respiration. Blood pressure was measured in two patients using a needle inserted in the brachial artery with the aid of an electro-manometer (Sanborn) and by the auscultation method in the third patient. Recording of blood pressure and of respiration was performed by a two-channel direct writer (Sanborn). The electrocardiograms were recorded by a Visocardiette. Ballistocardiograms were recorded in two patients.

During the examination the patients were recumbent, with the head in the central position. The tests were performed under the following conditions: (a) both eyes open; (b) both eyes closed; (c) alternate opening of

* From the Department of Nervous Diseases and the Cardiovascular Unit of the Rothschild Hadassah University Hospital and the Hebrew University Medical School.

each eye; (d) alternate placing of red and blue filters before each eye; (e) alternate turning of the head to the side of the disequilibrium (homolateral) and to the opposite side (contralateral) with eyes open or closed; (f) combination of changed head posture and application of coloured filters. The colour filters employed were Kodak Wratten, blue No. 47 and red No. 29.

Observations

Case 1. L. A., female, aged 42, presenting the sensorimotor induction syndrome in left-sided disequilibrium: In this patient the following neurological disturbances were present: (1) left-sided postural deviation of the whole body and the homolateral extremities; (2) left-sided visual displacement of spatial coordinates and geometrical figures, and micropsia when looking only with the left eye; (3) microstereognosis and underestimation of distances with the left hand; (4) influence of motor and sensory stimuli, including colours, on the disequilibrium and the induced sensory functions.

In this patient the sensorimotor disturbances were aggravated when both eyes were closed, when only the homolateral left eye was open, under the influence of the red filter, or when the head was turned to the contralateral right side. In contrast, a corrective influence was obtained when both eyes were open, when only the right contralateral eye was open, when a blue filter was applied or when the head was turned to the homolateral left side. These factors influenced the homolaterally disturbed statokinesis as well as the accompanying sensory disturbances.

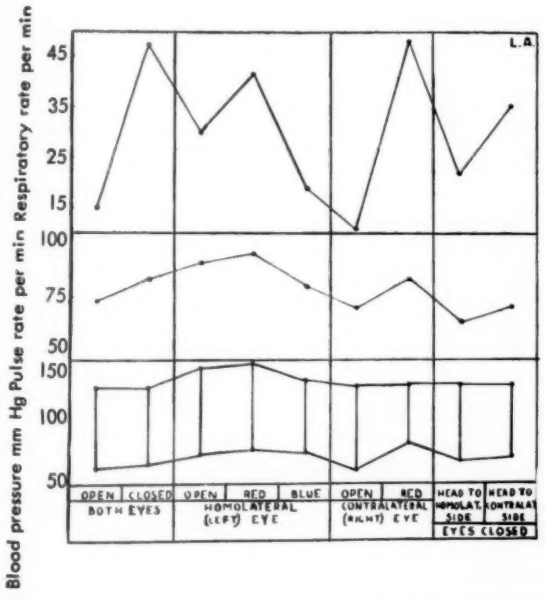

Fig. 1. Case 1, L. A. Changes in respiratory rate, pulse rate and blood pressure during closure of both eyes, alternate opening of each eye, turning the head to the side and under the influence of red and blue filters. See text for details.

The examination of the respiratory and circulatory functions which was performed under the above mentioned conditions showed the following results (Fig. 1):

When the patient, with eyes open, was resting in a supine position with the head in the central position, the respiratory rate was 15 per min, the pulse rate 75 per min and the blood pressure 128/64 mm Hg. The electrocardiogram was normal in every respect. Upon closing her eyes, the respiratory rate rose to 48 and became irregular; the pulse rate increased to 82, but the blood pressure showed no distinct change. When only the homolateral left eye was open, the respiratory rate was 30; the pulse rate 88 and the blood pressure 145/70. Placing the red filter before the left eye increased the respiratory rate to 42, the pulse rate to 92 and the blood pressure to 150/75. When the red filter was replaced by a blue one the respiratory frequency became 18, the pulse rate dropped to 80 and the blood pressure to 135/70. When only the contralateral right eye was open, respiration remained normal, 12 per minute, the pulse rate was 68 and the blood pressure 130/60. Placing the red filter before this eye changed the values as follows: respiration became irregular and its rate rose to 48, the pulse rate rose to 83 and the blood pressure was 130/80. The latter value was, however, of short duration and transitory.

When the head was turned to the homolateral left side, the respiratory rate was 24, the pulse rate 63 and the blood pressure 130/70. When the head was turned to the contralateral right side, however, the respiratory rate rose to 35, while the pulse rate and the blood pressure did not change. Except for the changes in the pulse rate the electrocardiogram showed no change during the whole experiment.

Case 2. S. S., female, aged 26, presenting the sensorimotor induction syndrome in right-sided disequilibrium: In this patient the following disturbances were present: (1) right-sided postural deviation of the whole body and the homolateral extremities; (2) right-sided visual displacement of spatial coordinates and geometrical figures and macropsia when looking with the right eye alone; (3) deviation to the right in tactile and haptic localization; (4) macrostereognosis and homolateral overestimation of weight when using the right hand; (5) influence of motor and sensory stimuli, including colours, on the disequilibrium and the induced sensory disturbances.

The sensorimotor disturbances were aggravated when both eyes were closed, when only the homolateral right eye was kept open, under the influence of a red filter and when the head was turned to the contralateral left side. In contrast, these disturbances were corrected when both eyes, or only the contralateral left eye were open, when a blue filter was used and when the head was turned to the homolateral right side.

Examination of the respiratory and circulatory functions under these experimental conditions showed the following results (Fig. 2):

When the patient rested in a supine position with her eyes open, the respiration was regular, 24 per min, the

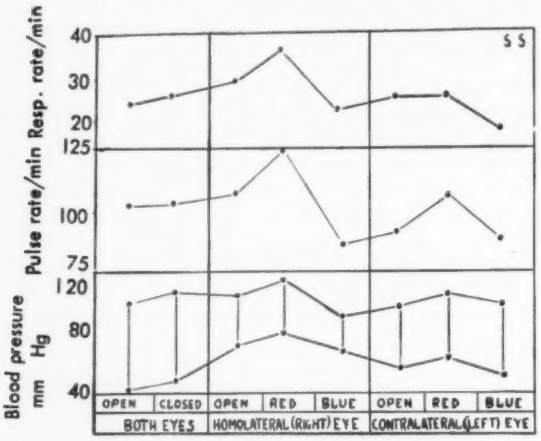

Fig. 2. Case 2, S. S. Changes in respiratory rate, pulse rate and blood pressure during closure of both eyes, alternate opening of each eye, and under the influence of red and blue filters. See text for details.

pulse rate was 103 per min and the blood pressure was 100/40 mm Hg. The electrocardiogram was normal. Upon closing her eyes, the respiratory rate was 26, the pulse rate 105 and the blood pressure 110/48. The T waves in the electrocardiogram became flat. When the homolateral right eye was open, the respiratory rate became 28, the pulse rate 108 and the blood pressure was 105/70. The T waves in the electrocardiogram remained flat. When a red filter was placed before the homolateral right eye, the respiratory rate became irregular and increased to about 36, the pulse rate rose to 125, the blood pressure to 115/85 and the T waves in the

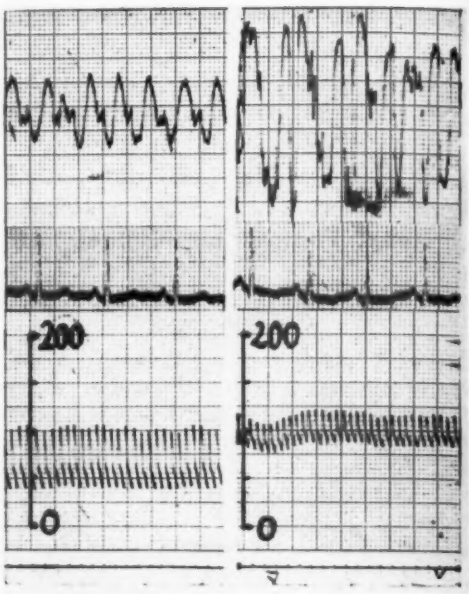

Fig. 3. Case 2, S. S. (A) Patient recumbent with eyes open and head in central position. Respiration (upper record) 24 per min, regular. Blood pressure (lower record) 100/40 mm Hg, pulse 103 per minute, electrocardiogram normal. (B) Red filter before right eye, head in central position. Respiration about 36/min, irregular, blood pressure 115/85 mm Hg, pulse 125/min, electrocardiogram shows inverted T waves.

electrocardiogram were isoelectric or inverted (Fig. 3). A marked change was observed when the red filter was replaced by a blue one. Respiration became regular, 24 per min, the pulse rate decreased to 85, the blood pressure to 90/70 and the electrocardiogram became normal. When the contralateral left eye was open, the respiratory rate was 26, the pulse rate 92, the blood pres-

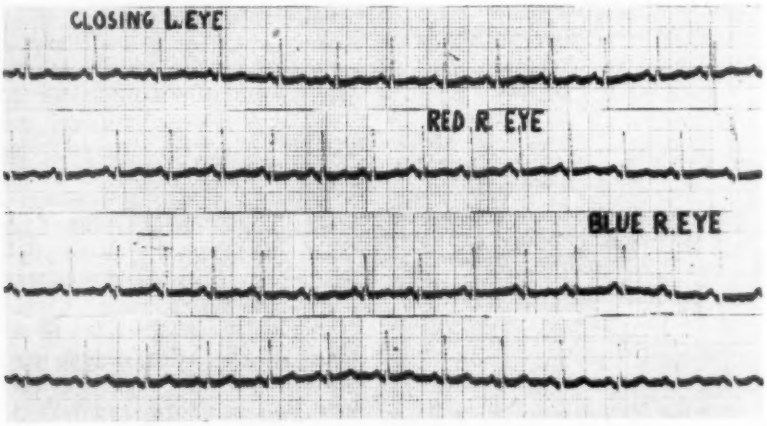

Fig. 4. Case 2, S. S. Flattening of T waves in the electrocardiogram after closure of the left-contralateral eye and under the influence of red. Effect reversed after the application of blue filter before the right-homolateral eye. Continuous record, lead II.

sure 100/58 and the electrocardiogram normal. Placing a red filter before this eye was accompanied by a rise in the pulse rate to 110 and in the blood pressure to 110/68 while respiration remained nearly unchanged. A slight flattening of the T waves was observed in the electrocardiogram. When the red filter was replaced by a blue one, the respiratory rate decreased to 18, the pulse rate to 88 and the blood pressure to 100/50. The T waves in the electrocardiogram became peaked upright. The effect of the coloured filters on the electrocardiogram are shown in Figure 4.

Further tests were performed in order to study the influence of head posture on the same functions (Fig. 5). When the patient rested in a supine position with her eyes open, the initial findings were as follows: respiration 23, pulse rate 88, blood pressure 120/68 and normal electrocardiogram. When the patient's head was turned to the contralateral left side, the respiratory rate became irregular and rose to about 42, the pulse rate rose to 115, the blood pressure to 135/75 and the T waves in the electrocardiogram became temporarily isoelectric (Fig. 6). Closing the patient's eyes in this condition brought about a further rise in the pulse rate to 122, respiration remained about 42, the blood pressure was 135/80 while the T waves in the electrocardiogram remained flat. Keeping this head position and placing a blue filter before the open left eye led to a decreased pulse rate of 95 and a decreased blood pressure of 125/62, although the respiration remained unchanged. The T waves in the electrocardiogram became upright. Turning the head to the right side with both eyes open was accompanied by a respiratory rate of 24, a pulse rate of 108 and a blood pressure of 125/60. The electrocardiogram was normal. When, in this condition, the patient closed her eyes the respiratory rate became 20, the pulse rate 90 and the blood pressure 125/65. The electrocardiogram remained normal. When a red filter was then applied to the homolateral right eye, respiration became irregular, 38 per min, the pulse rate was 108 and the blood pressure 140/70. The T waves in the electrocardiogram became flat.

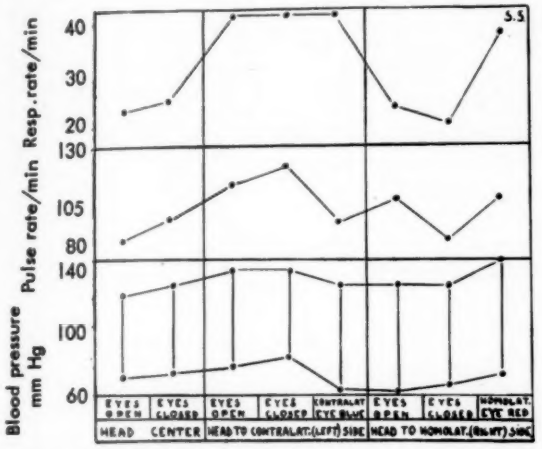

Fig. 5. Case 2, S. S. Influence of head position, with or without the application of coloured filters before the eyes, on respiratory rate, pulse rate and blood pressure. See text for details.

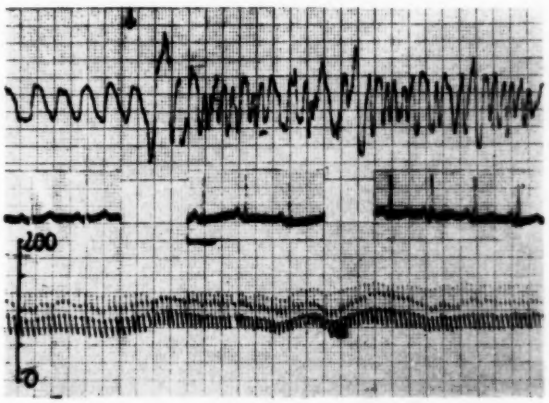

Fig. 6. Case 2, S. S. Influence of head position on respiration (upper record), blood pressure (lower record) and the electrocardiogram. During the control period respiration was 23/min, regular, the pulse 88/min, the blood pressure 120/68 mm Hg and the electrocardiogram normal. When the head was turned to the contralateral left side (at arrow) the respiration became irregular, about 42/min, the pulse 115/min, the blood pressure 135/75 mm Hg and the electrocardiogram showed flattening of the T waves.

The ballistocardiographic tracing of this patient, which was normal in the resting position, showed a disturbed heart action when the homolateral eye was open, when a red filter was placed before either eye, or when the head was turned to the contralateral side. During these conditions, the ballistocardiographic pattern became irregular, chaotic, and showed "respiratory variations" grade 2–3, even during held semi-inspiration (Fig. 7).

Case 3. G. B., female, aged 34, presenting the sensorimotor induction syndrome in left-sided disequilibrium: In this patient the following disturbances were present: (1) downwards and outwards deviation of the left arm and leg; (2) deviation to the left in haptic localization; (3) underestimation of the size of objects when using the left hand (microstereognosis); (4) influence of coloured filters on the motor and sensory disturbances.

Respiratory and cardiovascular functions were examined under the above mentioned experimental conditions with the following results (Fig. 8):

When the patient was resting in a supine position with her eyes open the initial values were as follows: respiratory rate 15 per min, pulse rate 80 per min and blood pressure 110/70 mm Hg. When only the homolateral left eye was open, respiration was 27, the pulse rate 92 and the blood pressure 115/73. When a red filter was

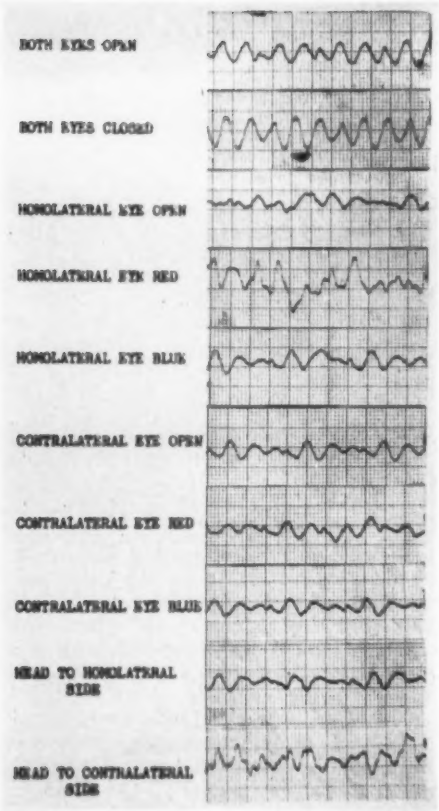

Fig. 7. Case 2, S. S. Ballistocardiographic records during the various experimental procedures. See text for details.

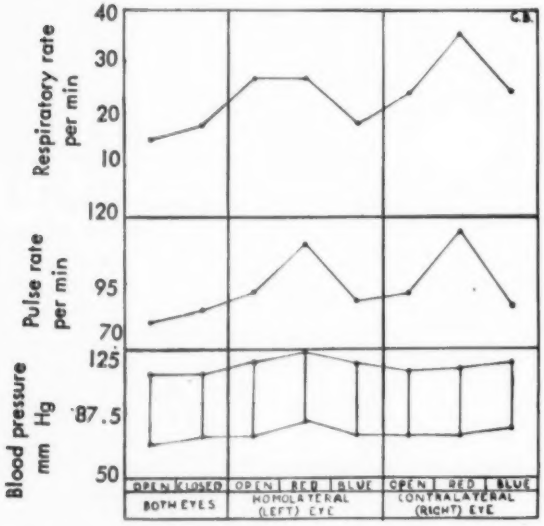

Fig. 8. Case 3, G. B. Changes in respiratory rate, pulse rate and blood pressure during closure of both eyes, alternate opening of each eye and under the influence of red and blue filters. See text for details.

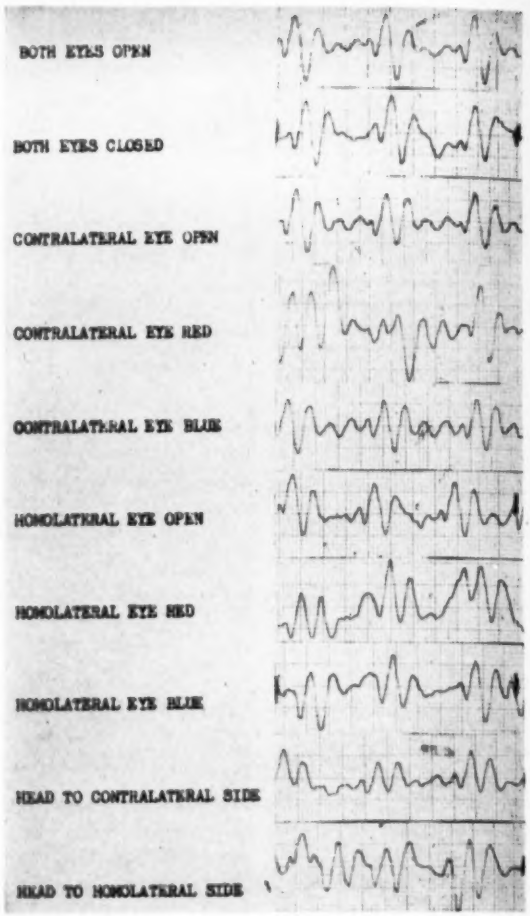

Fig. 9. Case 3, G. B. Ballistocardiographic record during the various experimental procedures. See text for details.

placed before the left eye, the respiratory rate remained 27, the pulse rate rose to 110 and the blood pressure to 125/85. Replacing the red filter by a blue one decreased the respiratory rate to 19, the pulse rate to 87 and the blood pressure to 115/75. When only the contralateral right eye was open the respiration was 24, the pulse rate 92 and the blood pressure 110/75. When a red filter was placed before the right eye, the respiratory rate rose to 36, the pulse rate to 115 and the blood pressure was 115/75. Replacing the red filter by a blue one decreased the respiratory rate to 25 and the pulse rate to 84; the blood pressure was 115/80. Change of head posture influenced only the respiratory rate which was 18 per min when the head was turned to the right and 27 per min when the head was turned to the left.

Electrocardiographic changes were not observed under the above mentioned conditions. The ballistocardiogram, however, which in the resting position was normal, became irregular with "respiratory variations" grade 2–3 when a red filter was applied on either eye, or when the head was turned to the left (Fig. 9).

Comment

Previous investigations have shown that the unilateral disequilibrium in the sensorimotor induction syndrome is influenced by certain motor and sensory stimuli. It was demonstrated that closure of both eyes, placing a red filter before either eye and/or turning the head to one side—usually to the contralateral side—aggravated the postural imbalance of the patients. On the other hand, opening both eyes, opening the contralateral eye alone, placing a blue filter before either eye and/or turning the head to the other side produced a partial or complete correction of the abnormal postural pattern. The corrective or aggravating effects of the coloured filters differed in degree depending on the eye in front of which the filter was placed. The red filter's aggravating influence was usually stronger when the filter was placed before the homolateral open eye since its effect was added to the aggravation produced by the opening of this eye alone. The greatest corrective effect was achieved by placing a blue filter before the contralateral eye as this corrective influence was added to the corrective effect produced by the opening of this eye. Furthermore the effect of the sensory stimuli of the colours appeared to be stronger than that of the motor stimuli of changed head posture.

It is of basic importance that the aggravation or amelioration of the disequilibrium, caused by the stimuli mentioned above, was accompanied by corresponding changes of visual functions, acoustic perception, stereognostic estimation of size, vibratory perception, two point discrimination and reaction time.[1–13] The present study demonstrates that the above mentioned experimental procedures also exert a profound influence on the respiration, pulse rate, blood pressure and the electrocardiogram. Changes in the breathing frequency and the pulse rate were noted in all three patients; the blood pressure changed significantly in one patient and less markedly in the other two. The ballistocardiogram showed a marked alteration in two patients, while the electrocardiogram became abnormal in only one patient. It is noteworthy that the patients were obviously disturbed during the application of the aggravating stimuli. In addition to tachypnea and palpitation, they sometimes experienced general discomfort, abdominal pain and nausea. The skin colour became pale. Emotional upset was evidenced by restlessness and occasionally by weeping. All these physical and mental manifestations disappeared rapidly when the corrective measures were applied.

The intimate mechanism by which the disequilibrium influences the respiratory and circulatory functions could not be clarified. It is probable that the central regulatory areas of the equilibrium, particularly the cerebellum, are involved in disturbances of the equilibrium in the sensorimotor induction syndrome. It should be borne in mind that the human equilibratory system does not depend on uninterrupted long tracts, but on the uniform and constant cooperation of several relay connections, one interlocking with the other. This system includes the vestibular nerve which is connected to the cerebellum by the vestibulocerebellar tract and to the spinal cord and the midbrain through its nuclei. In addition, there are reciprocal corticopontocerebellar connections interconnecting the frontal lobes of both hemispheres with the cerebellum. In this equilibratory system, which has only been mentioned here in a general way, the cerebellum seems to occupy the central position. In this connection the electroanatomic studies of Snider[14] who discovered visual, tactile and auditory areas in the cerebellum, are of special interest. On the basis of his investigations, Snider stated that the cerebellum acts both in motor and sensory spheres, and that these spheres do not subserve any known conscious function. Snider's findings correspond very well with the clinical observation that the induced unilateral sensory disturbances are unsuspected by patients suffering from unilateral disequilibrium. The widespread connections of the equilibratory system and especially the cerebellum, with the frontal lobes, the diencephalon and the mesencephalon, may provide the anatomical basis for the induction of respiratory and circulatory changes by unilateral disequilibrium. It may be that the induced respiratory and circulatory changes described above occur through the reflex stimu-

lation by the disturbed equilibrium of the autonomic centers. Hyperpnea, tachycardia, hypertension and T wave changes in the electrocardiogram have been produced experimentally by injections of adrenalin and noradrenalin,[16–18] as well as by electrical or heat stimulation of the white matter in the forebrain or the anterior hypothalamus.[19,20] A similar clinical syndrome may occur, as is known, during the paroxysmal attacks of pheochromocytoma.

Electrocardiographic changes similar to those observed in patient 2, have been described during self-induced hyperventilation.[21] This, however, does not seem to be responsible for the electrocardiographic changes in our patients since the changes were also noted under the influence of stimuli which did not markedly affect respiration. On the other hand, hyperpnea was sometimes observed without electrocardiographic changes.

A possibility to be considered is that the respiratory and circulatory disturbances appear as a nonspecific reaction to the stress or the emotional upset. Similar changes in respiration, pulse rate, blood pressure and in the electrocardiogram have been observed under the influence of pain, emotion and/or other stress situations.[22–25] This possibility, however, seems unlikely since the change of respiratory and circulatory functions is not an isolated phenomenon, but is a part of the systematically induced changes of sensory as well as autonomic functions.

Summary

Unilateral disequilibrium is sometimes accompanied by sensory disturbances dependent on the degree of the statokinetic disturbance. The postural pattern and the secondary sensory disturbances are ameliorated or aggravated by various motor or sensory stimuli. The name of "sensorimotor induction syndrome" has been applied to this clinical entity.

The respiratory and circulatory functions were examined in three patients presenting the sensorimotor induction syndrome in unilateral disequilibrium under the experimental conditions which were found to affect the statokinetic and the sensory functions. These conditions are: changing of head posture, bilateral closure of the eyes, alternate opening of each eye and the effect of red and blue filters when placed before the eyes. The examinations revealed that the experimental stimuli which caused deterioration of the basic statokinetic disturbance and of the concomitant sensory disturbances, cause an impairment of the respiratory and circulatory functions as well. This is manifested by tachypnea, tachycardia, rise of blood pressure, flattening of the T wave in the electrocardiogram and ballistocardiographic changes indicating myocardial dysfunction. Application of the factors which corrected the statokinetic and the induced sensory changes restored the respiratory and circulatory functions to normal.

These findings demonstrate that the inductive effect of unilateral disequilibrium influences not only the sphere of the somatic nervous system but, under certain conditions, the autonomic nervous system as well. The occurrence of such secondary induced alterations of the respiratory and circulatory functions, as an indirect result of the primary disturbed equilibrium, and the possibility of producing and correcting them by experiment, seems to be of special interest.

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Reviews

The Carotid Sinus Syndrome

SIEGFRIED SALOMON, M.D., F.A.C.C.

Staten Island, New York

THE ARTERIAL blood pressure regulatory mechanisms in man are not as yet fully defined. It has long been known, however, that the carotid sinus probably plays a major role. Functional aberrations of the reflex arc associated with the workings of the pressoreceptors in the carotid sinus give rise to clinical manifestations of the carotid sinus syndrome, characterized in general by bradycardia, hypotension and syncope.

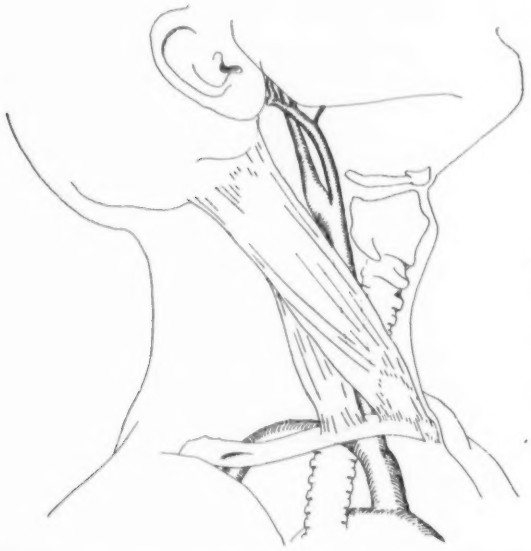

Fig. 1. The topographic location of the carotid sinus is illustrated in its site at the level of the thyroid cartilage in the angle between the larynx and the anterior margin of the sternocleidomastoid muscle.

HISTORICAL BACKGROUND

It is of interest that Galen was aware of the relationship between the carotid artery and syncopal episodes, stating that the vessel was so named because externally applied pressure produced *καρος* or deep sleep. This association must have been common knowledge in that ancient Assyrians are said to have utilized carotid artery pressure to provide analgesia during circumcision rituals.[3]

Parry[71] in 1799 restated the observation that pressure upon the carotid artery caused a slowing of the heart. The erroneous assumption that this was mediated by way of direct vagal stimulus was dispelled by the anatomic and physiologic studies of Hering,[40,41] who demonstrated succinctly that bradycardia was reflexly initiated from nerve endings in the carotid sinus. Section of the vagus nerve was demonstrated by Sollmann and Brown[95] not to affect the reflex blood pressure fall produced by traction on the cephalic end of a divided carotid artery. The problem was more clearly defined anatomically by the very fine investigations of de Castro[15] and Sunder-Plassmann,[98] and physiologically by Heymans and co-workers.[43–49]

ANATOMY

The carotid sinus is a short, thin-walled, slightly bulbous dilatation of the posterior aspect of the carotid artery situated bilaterally at its bifurcation into the internal and external carotid arteries. Occasionally the sinus dilatation may involve the beginning portions of the internal carotid as well. The wall of the sinus contains an extensive nervous network consisting of myelinated sensory receptor nerves terminating in menisci which lie between connective tissue fibers within the tunica adventitia. These

are the pressure receptors. The deficiency of muscle fibers in this area within the media, adjacent to the baroceptor structures, has suggested that the latter may be placed in series with muscle, particularly since adventitia and media are indefinitely fused.[7,55]

The afferent fibers of the meniscal proprioceptors ascend in the sinus nerve (sinus nerve of Hering, intercarotid nerve of de Castro) coursing between the internal and external carotids to join the glossopharyngeal nerve. Centrally these fibers end in the cardio-inhibitory and vasomotor medullary centers. Vagal and cervical sympathetic connections represent the main efferent pathways, the fibers joining the ganglion of the vagus nerve and the superior cervical ganglion,[9] respectively.

Topographically (Fig. 1), the carotid sinus is located in the anterolateral aspect of the neck at the level of the thyroid cartilage, in the angle between the larynx and the anterior margin of the sternocleidomastoid muscle.

Physiology

The sensory end-organs within the arterial walls of the carotid sinus are arranged in the adventitia in such a manner that they are stimulated by stretching of the vessel wall.[15] This stretching may be effected by an increase in the intra-sinal pressure secondary to generalized or focal elevation of the arterial blood pressure. Neurophysiologic investigations[9,49] have demonstrated continuous action currents in the sinus nerve, these apparently acting on the medullary centers to maintain cardio-inhibitory-accelerator and vasodilator-constrictor tonic balance. As pressure within the sinus rises, the frequency of action currents in the sinus nerve increases, causing imbalance in an unstable dynamic system. Thus the carotid sinus mechanism is a stabilizing influence on brainstem centers, counteracting overactivity of sympathetic functions in particular.[41]

In addition it reflexly influences the function of other organs, including the adrenal glands.[42] Experimental evidence exists to demonstrate that the secretion of epinephrine is diminished, respiration is depressed, skeletal muscle tone is decreased, gastric tone and motility are augmented, and bladder tone is diminished.[46,56] The respiratory reflexes noted to be initiated by stimulation of the carotid baroceptors[45] are contrary in effect to those brought about by stimulation of the chemoreceptors in adjacent carotid and aortic bodies. Whereas the latter causes an increase in the rate and depth of breathing, the former inhibits respiration, an abrupt increase in blood pressure producing apnea. In mammals, however, the pressoreceptors do not appear to serve any respiratory function under physiologic conditions.[6]

Both pressor and depressor effects may be mediated. This "buffer" mechanism is thought to be one of considerable importance in the control of the systemic blood pressure and the maintenance of adequate circulation to the brain. Brown and Hilton[10] have shown that the pressoreceptor reflexes are actually unable to maintain the blood pressure elevations caused by circulating epinephrine or secondary to rage and anger, thus indicating that the sino-aortic reflexes are more important within physiologic limits in their actions against hypotension. A drop in blood pressure in the carotid sinus subsequently results in acceleration of the heart rate, generalized vasoconstriction, and elevation of the systemic blood pressure. Moderate overresponse caused by generalized sympathetic reaction is the rule and gives rise to oscillating cyclic pressure changes (Traube-Hering or Mayer waves).[34]

The pressoreceptor system, in summary, acts to resist blood pressure changes. Abnormal responses to pressure changes give rise to the manifestations of the carotid sinus syndrome.

Pharmacology

The pattern of organ-system response to an increase in intrasinal pressure is that of stimulation of the parasympathetic nervous system. Contrariwise, a decrease of pressure within the carotid sinus results in sympathetic nervous system response.

Drugs which act primarily to elevate or depress systemic blood pressure will secondarily influence the pressoreceptors accordingly:

EFFECTS ON THE CAROTID SINUS OF VARIOUS AGENTS

Increased sensitivity	*Decreased sensitivity*
Light ether anesthesia	Deep inhalation anesthesia
Light vinethine	Atropine
Light nitrous oxide	Scopolamine
Light chloroform	Banthine[37,59]
Basal Avertin[51]	Quinidine[65]
Mecholyl[16,89]	Quinine
Physostigmine	Chloral hydrate
Digitalis[68,101]	Alcohol[18,24,26]
Morphine[82]	Caffeine (large doses)
Nicotine	Strychnine (large doses)[24]
Nicotinic acid[89]	Epinephrine
Thyroid extract	Ephedrine
Calcium gluconate	Benzedrine[81]
Insulin[83]	Paredrine
Salicylates	Neo-synephrine[30,32]
Potassium cyanide[64]	Isuprel[67]
Caffeine (small doses)	
Strychnine (small doses)[24]	*Unchanged sensitivity*
	Barium chloride
	Coramine
	Sodium lactate[5]
	Veratridine
	Potassium ion[4]
	Curare[12]

Anesthetic agents which locally denervate the sensory end-organs within the carotid sinus produce, in experimental studies, vasoconstriction and hypertension similar to that resulting from surgical sectioning of both sino-aortic nerves.[47] General anesthetics, however, act variably: moderate sensitization results from light ether, vinethene, nitrous oxide or chloroform anesthesia, and basal Avertin® anesthesia, while deep inhalation anesthesia decreases sensitivity.[51] Curare does not alter the reflex sensitivity.[12]

Autonomic blocking agents act to prevent sympathetic responses. These include atropine and scopolamine among the belladonna alkaloids, as well as related synthetic drugs, which inhibit structures innervated by postganglionic cholinergic nerves. An orally effective ganglionic blocking agent, Banthine (beta-diethylaminoethylxanthene-9-carboxylate), is capable of inhibiting the vasodepressor response.[37,59] Parasympathomimetic drugs, such as acetyl-beta-methylcholine (Mecholyl) and physostigmine, increase reflex sensitivity, acting by augmenting parasympathetic responses.[16,89] Sympathomimetic drugs including epinephrine, ephedrine, benzedrine,[87] Paredrine and Neo-synephrine[30,32] are effective in preventing asystole by inducing idioventricular rhythm, thus stimulating ventricular escape.

Digitalis has been found[68,101] to prolong periods of cardiac standstill, rendering the carotid sinus hyperactive. In addition, the carotid sinus is sensitized by morphine,[82] nitrites, nicotine and nicotinic acid,[89] thyroid extract, calcium gluconate, insulin,[83] salicylates and potassium cyanide.[64] Quinidine inhibits the motor effects of the sinus reflex.[65] Similarly, hyposensitization has been noted to result from chloral hydrate, quinine, and alcohol.[18,24,26] Variable responses have been detected from caffeine and strychnine,[24] small doses increasing sensitivity, larger doses decreasing it. No change in response occurs after barium chloride, Coramine, sodium lactate,[5] veratridine and potassium ion.[4]

Etiologic Factors

The hyperactive carotid sinus reflex as a clinical entity is well known but its cause is conjectural. Local sinus disease, once assigned as a major cause,[40,43] includes inflammatory changes in the regional nodes[52,62,76,102] and adjacent tumor masses. Autopsy studies,[53] however, have not borne out this contention, there being no discernible pathologic condition found in many cases. Reflex activity is perhaps enhanced by local adhesive processes, such as those secondary to previous inflammation or surgery, constricting overlying fascia or musculature, encroaching neoplastic mass, or anatomic abnormality of the carotid artery, including arteriosclerosis or aneurysm. Such abnormalities, however, may occur in the absence of an hyperreactive reflex.

The site of hypersensitivity of the abnormal reflex is not fully appreciated. Conceivably, it may be located anywhere along the reflex arc from the sensory receptors in the carotid sinus to the central synapses, the efferent neurones,[63] the extra- or intracardiac ganglionic cells, the myoneural junctions,[90] or the cardiac muscle itself.

The more frequent incidence of the clinical condition in the older age groups tends to support the thought that arteriosclerotic changes are among the possible etiologic factors. This

association with arteriosclerosis, hypertensive and coronary artery disease is rather well established.[92]

There have been cases reported of hypersensitivity associated with such sundry factors as biliary tract disease,[20,103] acute myocardial infarction,[13,91] glossopharyngeal neuralgia,[79,80] thrombosis of contralateral carotid artery,[29] esophageal traction diverticulum,[28] exposure to high altitudes and relative anoxemia,[70] and hypoglycemia.[36] In addition, brain lesions, such as central nervous system lues, brain tumor, and injury secondary to skull fracture, have been associated with a sensitive carotid sinus.[57,104]

Classic precipitating factors include manual, instrumental, and positional pressure on the carotid sinus. Most frequently reported are sudden movements of the head and neck, stooping over, standing erect, coughing, straining at stool, shaving, tight collars, and manipulation of the neck by surgeon, anesthesiologist, or chiropractor. Its association with tight collars has earned the clinical syndrome the name of "the minister's disease."[69] Sensitivity is also aggravated by emotional upsets and neurotic states.[22–24,26,102,104]

Clinical Picture

The triad of bradycardia, hypotension, and syncope characterizes the syndrome of the hypersensitive carotid sinus reflex. Three reflex mechanisms, each with corresponding distinctive manifestations, have been described.[102] These comprise the cardio-inhibitory or vagal, the vasomotor or vasodepressor, and the cerebral reflexes, respectively. Their differentiation is probably of little more than academic interest, particularly in view of the uncommon clinical occurrence of "pure" types alone.[26,30]

The cardio-inhibitory aspects of the reflex, mediated by way of the cardiac fibers of the vagus, vary with the pattern of the Purkinje conduction system involved.[65,74,102] Usually the sinoatrial and the atrioventricular nodes[96] are depressed and the atrioventricular conduction impaired, resulting in atrial or ventricular slowing or asystole and blocks of all degrees. Reflex changes in the coronary artery tonus have also been postulated.[102] Rarely, atrial flutter or fibrillation is produced by carotid sinus stimulation.[60] The resultant effects on cardiac function produce a decrease in cardiac output and secondary cerebral anoxia, the latter associated with syncope and occasionally convulsions.

The vasodepressor phase of the reflex, mediated via autonomic pathways, causes widespread vasodilatation and secondary hypotension independent of cardiac slowing. Symptoms resulting from inadequate cerebral blood flow are indistinguishable from those of the vagal reflex, although, in the former, they tend to be more prolonged.

The cerebral reflex results in syncope and convulsions without changes in blood pressure or pulse. Its mode of action is not clearly defined. It may be explained on the basis of reflex neurogenic stimulation of specific areas of the brain. Cerebral blood flow has been found unaltered.[30] No focal vascular changes have been demonstrated.[57] It has, however, been determined that even a completely anesthetized carotid sinus may produce cerebral symptoms, implying that these may be due to an impaired blood supply to the brain resulting from actual occlusion of the carotid flow.[77]

The diversified different pathways afford varying clinical pictures because of inconstant motor manifestations, and contralateral effects are found because of the decussation of nervous pathways. Thus, in addition to the cardiovascular involvement, the respiratory, gastrointestinal, pelvic organs, and the adrenal glands may be influenced.

Spontaneous attacks may be preceded by such prodromal symptoms as unsteadiness, weakness, blurring of vision, scotomata, tinnitus, nausea, epigastric distress, a feeling of epigastric emptiness or bloating, dizziness, vertigo, light-headedness, and faintness. In addition, visual or auditory hallucinations, and facial or extremity paresthesias may be noted. The latter include numbness, tingling, or pricking, and occur on the side opposite to the stimulated sinus. Occasionally temporary blindness occurs in one or both eyes. Abortive attacks may subside before unconsciousness supervenes.

Syncope occurs abruptly or gradually and is of short duration, lasting usually but a few minutes. It is associated with pallor, followed by facial flush and profuse perspiration, slow shal-

low respirations, dilated pupils, and generalized flaccidity. Postsyncope confusion is mild and brief, and is associated with lassitude and anxiety. In the cerebral type, however, the residua may persist for several hours. Convulsions may follow shortly after the onset of the unconscious state, or, in the cerebral reflex, may precede the syncopal attack or occur alone. Convulsions are clonic in nature, and often unilateral. Tongue-biting, loss of sphincter control, postictal amnesia, and headache are rarely seen.

Diagnosis

Diagnosis is based on the history of typical recurrent short-lived syncope attacks and the exact reproduction of the attacks by digital pressure on the carotid sinus. The latter consideration is particularly important in view of the relative frequency with which asymptomatic hypersensitive carotid sinus reflexes occur, and the fact that symptoms may follow sinus pressure in patients who do not spontaneously exhibit attacks. Suspicion should be aroused when attacks are noted in males in the sixth and seventh decades, these being especially liable to exhibit the conditions.[18,22,23,66,87,93,94]

Carotid sinus pressure should be applied with the patient in a sitting position, preferably unsupported, so that he may promptly be laid supine should syncope supervene. The patient's head is tipped back slightly and turned away from the side to be tested. Pressure is administered from behind with the ball of the thumb gradually compressing the carotid sinus posteriorly against the transverse processes of the cervical vertebrae. Massage enhances the effect, and may be employed with caution. Unduly prolonged or bilateral stimulation should be avoided. Frequent or continuous blood pressure, pulse, and electrocardiographic observations are of considerable importance in evaluating responses.

Syncopal attacks may be induced during digital carotid sinus stimulation used therapeutically in paroxysmal atrial tachycardia[54,73,85] Although usually followed by prompt and complete recovery, spontaneous and more especially induced attacks, particularly if prolonged, may lead to dangerous or even fatal complications. Many otherwise unexplained surgical deaths may be due to prolonged reflex asystole.[17,25,35,82,84,100,105] Serious neurologic sequelae are not unknown.[2,8,21,27,61,62] It is, therefore, obvious that carotid sinus pressure should not be injudiciously attempted for diagnosis or therapy in the face of known heart disease or arteriosclerosis, or in the elderly unless clearly indicated.

Hysterical reactions should be ruled out by pressing on parts of the neck other than the carotid sinus areas. In addition, anesthetization of the sensitive sinus with local novocaine solution injection will add confirmatory evidence if successful in eliminating the previously elicited syncopal response.

Fig. 2. Cardiac standstill of 4.8 seconds' duration has been produced after slight pressure applied to the right carotid sinus region. The patient complained of severe chest pain during this episode. (Courtesy of Dr. Jacob J. Silverman, Staten Island, N. Y.)

Characteristic electrocardiographic changes have been noted during carotid sinus stimulation.[31,38,58,74,88] These include ventricular asystole resulting variably from sino-atrial arrest (Fig. 2) or atrioventricular block; sino-atrial bradycardia; P-R interval prolongation; and diminution in the amplitude of the P waves. The QRS complexes remain essentially unchanged, indicating the expected anatomic distribution of vagal fibers limited mainly to the atria. Contrary evidence has been reported.[50] T wave alterations have also been found,[1,19,31] believed to be due to influences on the speed of repolarization of the myocardial conduction system. None of the changes noted, however,

can be considered diagnostic, there being no clear-cut correlation with symptoms.

Therapy

Mild attacks generally require no special immediate therapy, the episode usually having subsided prior to the attendant's arrival. For more severe symptoms or for frequently occurring attacks, active measures must be taken. The patient should be warned to avoid sudden movements of the head and neck, or any constriction or pressure on the neck. Detection and treatment of local conditions in the carotid sinus area may occasionally be effective in eliminating mechanical sources of pressure.

Drug therapy for the prevention of attacks has not proved universally satisfactory. The drug in widest use is atropine sulphate in 0.5 mg doses three times daily. Mild sedation may be required to allay apprehension. Other drugs in wide use include epinephrine, ephedrine, and related agents. Increasingly popular has been the use of Banthine[37,59] in 50 to 200 mg oral doses daily. Isopropyl norepinephrine (Isuprel) has recently shown promise[67] as an effective agent.

Intractable cases which may be incapacitating and which have had a thorough trial of medical management may be aided by surgical denervation of the carotid sinus.[14,69,72,75,99] This has been moderately successful, but is not a completely harmless technic. Anticipated effect should be determined prior to surgery by local anesthetic injection. Where surgical denervation has failed, or where local diseases make carotid sinus surgery impracticable, intracranial section of the glossopharyngeal nerve has been demonstrated to be quite successful,[11,39,77–80] although it results in nasopharyngeal anesthesia and the loss of taste perception in the posterior third of the tongue. Currently, x-radiation of the sensitive sinus has proved a less radical and equally effective method for dealing with this problem.[33,97]

For attacks occurring while the patient is under anesthesia, prompt therapy is necessary to prevent fatality or serious neurologic sequelae. Surgery and anesthesia should be discontinued immediately, pressure on the neck released if present, an airway established and oxygenation maintained, and procaine injected locally into the carotid sinus.[25] Routine preoperative testing and, if sensitivity be demonstrated, prophylactic local procaine infiltration may avoid this potentially tragic event.

Summary

(1) The clinicopathologic manifestations of the carotid sinus syndrome have been reviewed.

(2) The anatomy, physiology, and pharmacology of the carotid sinus are detailed.

(3) Methods of diagnosis are presented.

(4) Particulars of medical and surgical technics of treatment are outlined.

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The Treatment of the Carotid Sinus Syndrome*

ROBERT E. ROSCOE, M.D., CONSTANTINE P. FALLER, M.D., *and* KENNETH E. QUICKEL, M.D.

Harrisburg, Pennsylvania

EVER SINCE Hering[1] conclusively demonstrated in animals that slowing of the heart and other effects of carotid sinus pressure are due to reflexes arising in the carotid sinus, there has been a marked interest in this mechanism as a readily demonstrable etiologic factor in certain cases of syncopal or convulsive attacks. Weiss and his co-workers[2,3] placed these observations on a firm clinical basis and differentiated them into three clinical types. This report concerns five patients observed by the authors in the past year. A pertinent review of the literature and the pathologic physiology will be attempted before presentation of the cases.

ANATOMY AND PHYSIOLOGY

The carotid sinus is a bulbous dilatation of the first portion of the internal carotid artery. The tunica adventitia of the sinus is thicker than the tunica adventitia of the rest of the artery, and contains special nerve cells or "nerve receptors" situated between the layers of collagen. Pressure-sensitive fibers of the glossopharyngeal ("nerve of Hering"), hypoglossal, vagal, and cervical sympathetic nerves are generally believed to carry afferent impulses to the vasomotor and cardio-inhibitory centers in the reticular formation of the medulla.[4] From here the impulse traverses the central synapses and, after crossing, passes contralaterally as a motor impulse toward the periphery through widespread autonomic nerve pathways, namely the vagus, the sympathetics, and the central motor pathways. The type of response, therefore, depends primarily on the direction of the motor responses induced.

Normally, the carotid sinus is concerned with regulation of blood pressure and cardiac rate, and mechanical pressure will cause slight slowing of pulse with concomitant slight fall in blood pressure. In patients in whom the carotid sinus reflex mechanism is abnormally sensitive, however, mechanical stimulation produces marked symptoms.

The first type of carotid sinus syndrome is the vagal type in which the symptoms result from cardiac slowing or asystole. The efferent impulse travels over the vagus nerve to set up a heart block. These impulses may be blocked with atropine. The second or depressor type is mediated via the vasomotor center and sympathetics to produce vasodilation with hypotension entirely unrelated to cardiac slowing. Ephedrine may help in the therapy by causing vasoconstriction whereas atropine is of no benefit. The third type of carotid sinus syndrome is the cerebral type where the symptoms result apparently from impulses which travel directly to the brain. No significant changes occur in the heart rate or the blood pressure. Local alterations in cerebral circulation may be the cause of symptoms.[5]

CLINICAL PICTURE

Although a variety of symptoms are to be found in this condition, the typical patient presents himself with the chief complaint of attacks of vertigo and spells of unconsciousness. A definite aura is usually present consisting of weakness, lightheadedness, spots before the eyes and epigastric distress. Classically, these attacks are precipitated by the wearing of stiff collars,

* From the Department of Cardiology, Harrisburg Hospital, Harrisburg, Pennsylvania.

sudden turning of the head, straining at stool, shaving, or even coughing may be the trigger mechanism. In most instances the precipitating factors are unexplained.[6] Sigler[7] in a large series of cases found that the symptoms produced in order of frequency were dizziness, unconsciousness and convulsions, abnormal sensations referable to the eyes, the vasomotor system, the sweat glands, the organs of sensation, the respiratory system, the somatic muscular system, the general constitutional state, the gastrointestinal system, and the heart.

Carotid sinus syncope is much more common in males than females. The ratio in one Mayo Clinic series was 5 to 1 as reported by Smith.[6] It is most common among middle-aged and elderly persons; it is rare among young people. Local abnormalities such as carotid body tumors, atherosclerosis and lymph nodes were emphasized by earlier authors; however, later reports depreciate the influence of local factors.[9] The presence of coronary artery disease is felt by some authors, especially Sigler,[7,10] to be an important factor if not the cause of the carotid sinus syndrome. Local ischemia, he believes, either diminishes the resistance of the ganglia and the myoneural junctions in the heart or produces local chemical changes that sensitize the vagus system in the heart. It is worth noting that many patients with a hyperactive carotid sinus show evidence of coronary artery disease.

Diagnosis

The diagnosis, if suspected, is relatively easy as outlined by Askey.[8] With the patient in an upright position a steady pressure is exerted on the carotid sinus for 10 to 15 sec. Both sides should be tested in turn but the right is the common offender. Bilateral carotid sinus stimulation may be dangerous. A positive response to carotid sinus stimulation would be reduplication of some or all of the patient's symptoms. Giddiness, blurring of vision, loss of consciousness, and even convulsions may occur. The examiner may note pallor, sweating, stare, and twitching or convulsive movements. In order to clarify the mechanism involved, blood pressure and pulse measurements are recorded before and after carotid sinus stimulation. An electrocardiographic tracing during an attack is also of inestimable value.

If auscultation of the heart or the electrocardiogram discloses marked cardiac slowing or asystole the case obviously fits into the first or vagal type as previously described. A relatively normal heart rate with a marked drop in blood pressure points to a vasopressor mechanism. If both blood pressure and pulse remain normal a cerebral mechanism is involved. The proper classification as to mechanism is of more than academic interest since the type of drug therapy that can be expected to lessen symptoms depends on the mechanism involved as was previously indicated.

Treatment

Therapy is directed at abolishing or reducing to a minimum the number of attacks. Mechanical factors such as tight collars should be eliminated. The patient should be instructed to avoid sudden turning of the head or strain on the neck muscles.

Reports vary on the efficacy of other methods of therapy, such as various drugs and surgery. The most commonly recommended drugs are phenobarbital, ephedrine, benzedrine and atropine. Haymond and Bellet[16] have recently demonstrated the value of Banthine in abolishing vagal impulses from carotid stimulation. At the Mayo Clinic, Smith[6] states that drug therapy has not been particularly satisfactory but, of the drugs used, phenobarbital has given the best results. Draper[11] presented a series of eleven cases, all of which responded satisfactorily to therapy with extract of belladonna with or without phenobarbital in that no further attacks of fainting occurred. Rogers[12] reports three cases with good results from atropine and one poor response, despite pushing the drug to toxicity. All of the patients in the latter two series were in the first or vagal type of carotid sinus syndrome. Weiss[2] states that atropine sulfate in a dose of 0.5 mg three to four times a day by mouth, usually prevents spontaneous symptoms in the vagal type. He believes that ephedrine sulfate, 15 mg three to four times a day, will prevent attacks due to the depressor type. The exact value of drug therapy, however, remains controversial.

The benefits of surgical procedures are equally controversial. Weiss[2] reports good results in eight out of ten cases with adventitial stripping of the carotid bulb. Cattell[13] reports three cases successfully treated by adventitial stripping and sectioning of the carotid sinus "nerves." Turner,[14] in England, did a bilateral surgical procedure with good results. Craig and Smith[15] obtained excellent results in four cases, good results in one, fair in four, and poor results in four.

On the other hand, Sigler[7] believes that since the physiologic disturbances responsible for the manifestations of the hyperactive carotid sinus reflex appear to occur in the central neurons, surgery of the carotid sinus region cannot be expected to relieve many cases. Smith,[6] at the Mayo Clinic, states that although surgical treatment may be tried in selected cases, the results are not too satisfactory. All authors agree, however, that surgery should be tried in those cases where medical therapy has not helped.

Case Histories

Case 1. A 57-year-old white male executive was in good health until May, 1953. At that time he first experienced attacks of lightheadedness, dizziness, and weakness preceded by an aura of blurred vision. His family reported that his complexion would become florid, followed by an ashen gray color and unconsciousness. These attacks would last only a few minutes but were followed by a feeling of weakness lasting two hours. At first, attacks occurred every two to three weeks but became increasingly frequent so that during the week of admission several a day was the rule. The patient could not relate these attacks to sudden turning of the head or straining of neck muscles. In September, 1953, he was studied in another hospital with negative results. Past medical history and systemic review were otherwise noncontributory.

Physical examination was unrevealing; pulse 80, blood pressure 160 systolic, 100 diastolic. Routine laboratory work including complete blood count, urinalysis, fasting blood sugar, blood urea nitrogen, spinal fluid studies, and serology were all within normal limits. Blood cholesterol was 289 mg %. Chest x-ray and resting electrocardiogram were negative.

Light pressure on the right carotid sinus in the sitting position produced an immediate unconscious state with frank convulsions. Left-sided pressure had no effect. An electrocardiographic tracing during light pressure on the right sinus demonstrated cardiac asystole (Fig. 1a). The patient was in the supine position and the pressure was not maintained sufficiently long to produce unconsciousness or convulsions. Subjectively, he experienced dizziness and lightheadedness which reduplicated his admitting symptoms. It is interesting that an x-ray of the neck showed calcifications in the area of the right carotid bulb.

Next we were anxious to determine the effect of atropine. The following tests were therefore performed using electrocardiographic control to determine the exact moment of cardiac asystole. Atropine sulfate, 0.4 mg intramuscularly, was given. In exactly 30 min right carotid pressure was applied and resulted in cardiac asystole. Atropine sulfate, 0.4 mg, was then given intravenously. In 15 min heavy pressure on the right carotid sinus produced no effect on the cardiac rate (Fig. 1b).

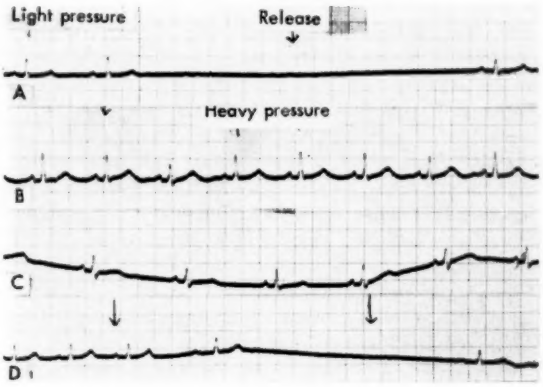

Fig. 1. Electrocardiogram of case 1. (A) Cardiac asystole during light pressure on the right carotid sinus. (B) Lack of effect of carotid sinus pressure following intravenous atropine. (C) Tracing taken during surgery on the carotid sinus. (D) Effect of carotid sinus pressure four months postoperatively.

The vagal impulses had been blocked. Approximately one and one-half hours later light pressure on the right sinus again produced cardiac asystole.

In view of the extremely heavy doses of atropine required to block the vagal impulses and the transitory benefit obtained, it was decided to treat this patient surgically. Therefore, adventitial stripping of the carotid sinus was carried out under local anesthesia using procaine infiltrations of the carotid bulb and intravenous atropine to reduce vagal impulses during surgery. The arteriosclerotic plaque reported by x-ray was palpated on the posterior surface of the carotid bulb. Continuous electrocardiographic tracings during surgery demonstrated a cardiac slowing to rate 48 but no other abnormalities (Fig. 1c). Five days postoperatively heavy pressure on the right sinus failed to produce any cardiac effect.

Four months after surgery the patient was carefully re-examined. He was working regularly and doing well except for occasional (one per month) attacks of blurred vision. These were very transitory and not followed by any further symptoms. However, very heavy pressure on the right carotid sinus again produced cardiac asystole (Fig. 1d).

It would appear, therefore, that although a good clinical response was obtained the hyperactive carotid sinus mechanism remained intact after surgery. Its excitability, however, was reduced since the pressure stimulus required to elicit response was much greater than previously. This was confirmed by the marked clinical improvement. Surgery, therefore, was of distinct value in the treatment of this patient despite the fact that cardiac asystole could still be produced under laboratory conditions.

Case 2. A 65-year-old white male executive was in good health until approximately three months prior to admission when he first developed "fainting spells." These attacks of unconsciousness were marked by generalized convulsions according to the family and lasted one to two minutes. They were not related to turning of the head or any precipitating factor known to the patient. The patient had an average of one attack per week until the week of hospitalization when four occurred. The physical examination was unrevealing; blood pressure was 180 systolic and 90 diastolic, pulse 82. Routine laboratory work including urinalysis, complete blood count, fasting blood sugar, blood urea nitrogen, chest x-ray and skull x-ray were within normal limits. The electrocardiogram disclosed a right bundle branch block with premature ventricular beats and a spontaneous paroxysmal 2:1 A-V heart block.

Pressure on the right carotid sinus in the sitting position reduplicated the patient's symptoms with unconsciousness and convulsions. Electrocardiographic tracings during pressure on the right sinus produced an atrioventricular block with ventricular arrest (Fig. 2). Atropine sulfate, 0.6 mg, was given intravenously. After 15 min pressure was again exerted on the right sinus. A slight slowing of the heart rate was demonstrated by the electrocardiogram but no further effect could be obtained.

It was decided in view of the sensitivity of the carotid sinus that surgical denervation was indicated. This was performed under local anesthesia using procaine infiltration of the carotid bulb and intravenous atropine sulfate. During the procedure the patient developed a sinus bradycardia rate 48 with a 2:1 heart block. Immediately following surgery the rate was 90 with a normal sinus rhythm.

A follow-up examination four months after surgery disclosed a good clinical response. The patient was working and asymptomatic. He denied any lightheadedness or other symptoms. Electrocardiographic tracings during pressure on the right carotid sinus demonstrated a marked sinus slowing of the heart rate but despite very heavy pressure atrioventricular block could not be produced as it easily was before operation.

In this case an excellent surgical result was obtained as verified by clinical and laboratory evidence. It was our impression at the time of surgery that the adventitial stripping was more complete than in the first case. This may account for the apparent better result and emphasizes the importance of doing a thorough adventitial stripping.

Case 3. A 39-year-old white policeman three years ago first noted lightheadedness and spots before his eyes on sudden turning of the head to the right. The patient never lost consciousness and symptoms disappeared as soon as the head was turned forward. His uniform called for a high collar. The patient also noted anginal symptoms for the past two years. Remainder of the history was negative. Physical examination was unrevealing. Blood pressure was 152 systolic and 88 diastolic, pulse 76. Routine urinalysis, complete blood count, and chest x-ray were within normal limits. Basal metabolic rate was −13. An electrocardiogram disclosed a right bundle branch block pattern without other changes (Fig. 3).

Pressure on the left carotid sinus reproduced the patient's symptoms. Pressure on the right sinus had no effect. Electrocardiographic tracing during pressure on the left sinus demonstrated very slight slowing of the heart. There was no change in blood pressure during

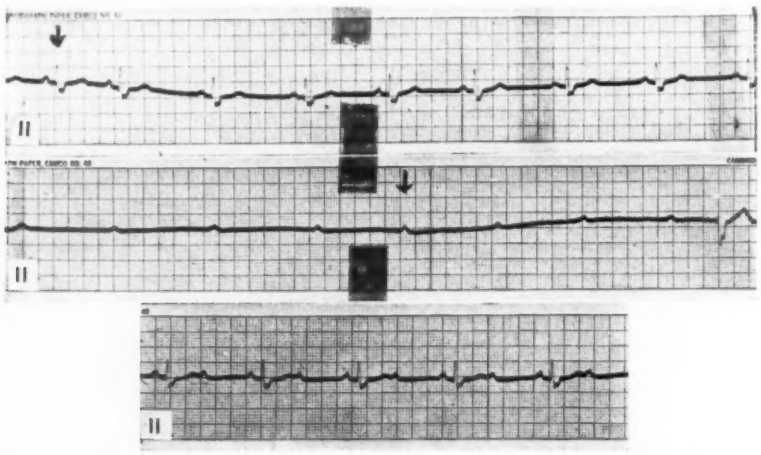

Fig. 2. Electrocardiogram of case 2 showing A-V block with ventricular asystole produced by right carotid sinus pressure.

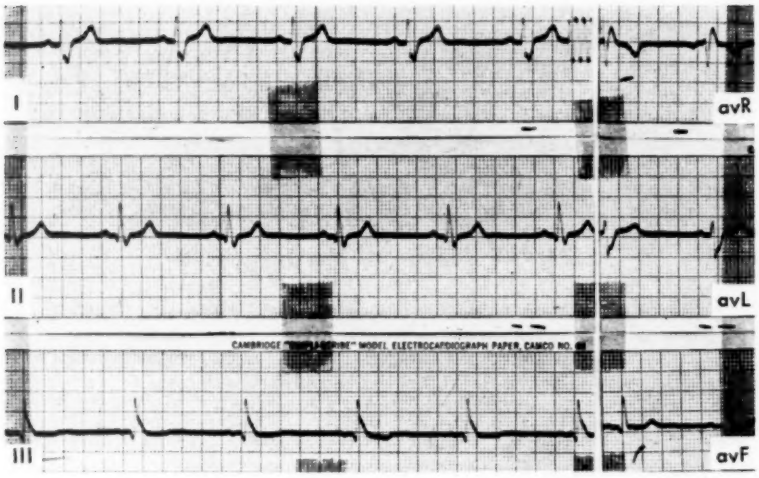

Fig. 3. Electrocardiogram of case 3 showing right bundle branch block.

the procedure. A diagnosis of carotid sinus syndrome of the cerebral type was therefore made. The patient was advised to wear loose collars and to avoid sudden turning of the head and straining of neck muscles.

Four months later a follow-up examination revealed that the patient was doing well. He has had no recurrence of symptoms. Pressure on the left sinus again reproduced his symptoms without change in pulse or blood pressure. This patient obtained a very good result merely by avoiding those mechanical factors which precipitated an attack. He illustrates the importance of carefully instructing patients to avoid those actions which cause symptoms.

CASE 4. A 54-year-old white postman first noted lightheadedness and dizziness in 1944. These attacks occurred while the patient was carrying a heavy mail bag on his left shoulder. His uniform called for a tight collar and the heavy bag pulled this collar against the right side of the neck. The patient would immediately drop the bag with disappearance of his symptoms. The patient had one attack while in the barber chair. He could not relate any attacks to turning of the head. There was no loss of consciousness or convulsive seizures. These attacks occurred with increasing frequency until two to three a week were not uncommon. He consulted various physicians over a period of 3 years without relief.

Physical examination was essentially negative. Blood pressure was 120 systolic and 80 diastolic, pulse 74. A routine electrocardiogram was negative. Pressure on the right carotid sinus reduplicated the patient's symptoms and in addition unconsciousness and convulsions were produced. Electrocardiographic tracings during sinus pressure revealed cardiac asystole (Fig. 4).

The patient was advised to wear loose collars. He resigned his position as a mail carrier and was trained as a machinist. In addition atropine sulfate, 0.4 mg, and phenobarbital, 30 mg, were given three times a day.

Repeated follow-up examinations over a period of years revealed the patient to be working regularly and to be asymptomatic. He denies any spontaneous symptoms; however, pressure on the right carotid sinus continued to produce symptoms with electrocardiographic evidence of cardiac asystole. The hyperactive carotid sinus mechanism, therefore, is intact but easily controlled with drug therapy.

This patient obtained a good result with drug therapy and elimination of possible mechanical precipitating factors.

CASE 5. A 56-year-old white school teacher first noted attacks of lightheadedness approximately three months prior to being seen. These attacks were precipitated by sudden turning of the head while wearing a tight collar.

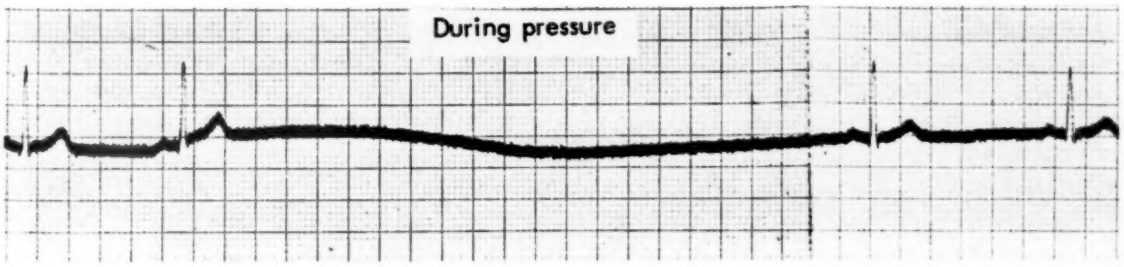

Fig. 4. Electrocardiographic tracing of case 4 showing cardiac asystole during right carotid sinus pressure.

They also occurred frequently while the patient was tightening his tie. There was no loss of consciousness or convulsions. He averaged about one attack per day. The remainder of the medical history was non-contributory.

The physical examination was entirely negative. Blood pressure was 132 systolic and 80 diastolic, pulse 84. A complete blood count and urinalysis were normal. A resting electrocardiogram was within normal limits.

With the patient in the sitting position light pressure was exerted on the right carotid sinus. Within 10 sec the patient became cyanotic, unconscious, and developed a generalized convulsion lasting one to two minutes. Recovery was prompt and complete. This attack was associated with cessation of the pulse. He has never developed a spontaneous attack as severe as was experimentally produced, but the lightheadedness that preceded his loss of consciousness reduplicated his symptoms.

The patient was unwilling to permit further sinus pressure with simultaneous electrocardiographic tracings, so we were unable to further classify the exact mechanism involved. It seems likely, however, that he would fit into the vagal type of carotid sinus syndrome because of the absent pulse and the severity of symptoms.

The patient was advised to wear loose collars and avoid sudden turning of the head or strain on the neck muscles. Two months later the patient was again examined. He has had only one attack of lightheadedness which occurred while he was tightening his tie. He again declined to submit to further sinus pressure, but it seems likely that the hyperactive carotid sinus mechanism remains intact.

Here again we have a good result by merely eliminating those mechanical factors which precipitate the attacks. If necessary, drug therapy can always be added at a later date.

Summary and Conclusions

(1) A brief review of the pathologic physiology involved in the carotid sinus syndrome is given describing the three mechanisms which are known to occur.

(2) The importance of determining the exact mechanism involved in the production of symptoms is emphasized since the type of drug therapy employed depends thereon.

(3) Five new cases of the carotid sinus syndrome are presented. The mechanism involved in each case is demonstrated. All patients obtained good clinical results; two from surgery and three from medical therapy.

(4) It is our impression that a hyperactive carotid sinus mechanism may explain many cases of apparently puzzling syncope. This condition is undoubtedly more common than formerly believed, and since the diagnosis is relatively easy, should be investigated in all cases of unexplained syncope and dizziness.

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Experimental Studies

Cardiac Dynamics and Coronary Blood Flow Consequent to Acute Hemorrhage*

STEVEN M. HORVATH, PH.D., F.A.C.C.,† E. ALLBAUGH FARRAND, M.A., *and* B. K. HUTT

Iowa City, Iowa

RECENT investigations into the behavior of the coronary circulation during hemorrhagic shock have been conducted by Opdyke and Foreman[1] and Edwards *et al.*[2] In their studies animals have been bled to a low arterial pressure and maintained in a stable hypotensive state for a prolonged period. Cardiac output and coronary blood flow were greatly diminished. Although there was a reinfusion of blood with a resultant rise in systemic blood pressure, the coronary blood flow and cardiac oxygen consumption remained considerably below control levels.

Since the above experimental conditions are rather severe, it was deemed worthwhile to evaluate these parameters in animals subjected to a single massive hemorrhage which offered the opportunity for successful physiological readjustments.

METHODS

Ten experiments were conducted on ten mongrel dogs ranging in weight from 12.6 to 28.7 kg (mean body wt. 19.9 kg). The animals were anesthetized with sodium pentobarbital (30 mg/kg body weight) and heparinized (5 mg/kg body weight). A single lumen cardiac catheter was inserted into a branch of an external jugular vein and guided with fluoroscopic aid into the coronary sinus. A second cardiac catheter was inserted into a second branch of the jugular vein and positioned in the main pulmonary artery. A branch of the femoral artery in one limb was cannulated for pressure tracings and sampling purposes; the femoral artery in the opposite limb was cannulated for bleeding. Blood pressures were recorded continuously throughout the experiment with Statham strain gauges and appropriate amplifying and recording equipment from the femoral artery, coronary sinus, and pulmonary artery. The point of zero reference for all blood pressures was the right atrium. Oxygen consumption was determined from expired air samples collected in a Tissot spirometer and analyzed for oxygen content in a Beckman oxygen analyzer. Coronary blood flow was determined by the nitrous oxide technic modified slightly[3] from the method of Kety and Schmidt.[4] A mixed venous sample was obtained from the pulmonary artery during the middle of the coronary flow samples. All blood samples were analyzed for nitrous oxide content by the method of Orcutt and Waters[5] and oxygen content by a modification of the method of Van Slyke and Neill.[6] Hematocrits were determined by the Wintrobe tube technic.

Following the withdrawal of samples for control determinations the animal was bled from a femoral arterial cannula. A blood volume equivalent to 4 per cent of the animal's body weight was allowed to flow rapidly from the vessel. The average time required for bleeding was 14.3 minutes. Blood samples for the determination of cardiac output and coronary blood flow were taken immediately and at one hour after completion of the hemorrhage.

Upon completion of each experiment the animal was given 300,000 units of penicillin, intramuscularly, and returned to its cage and kept under observation. At least two months were allowed for recovery before the animal was used for further experimentation.

Cardiac output was calculated by the direct Fick principle. The oxygen consumption of the left ventricle, left ventricular work, aerobic energy uptake of the left ventricle and mechanical efficiency were determined by the equations of Bing *et al.*[7] Coronary vascular resistance was obtained by the formula:

$$\frac{\text{mean arterial pressure-mean coronary sinus pressure}}{\text{coronary blood flow (ml/100 g left vent/min)}}$$

* From the Department of Physiology and Cardiovascular Laboratory, College of Medicine, State University of Iowa, Iowa City, Iowa. This investigation was supported in part by the Medical Research and Development Board, Office of the Surgeon General of the Army under Contract No. DA-49-007-MD-150.

† Presently at Lankenau Hospital, Philadelphia.

Results

Seven of the ten experimental animals survived the experiment, one animal was sacrificed for other purposes and two expired during the procedure (Table I). One of the latter was inadvertently hemorrhaged an additional amount near the end of the experiment, a possible cause of death. No animal received a reinfusion of blood or any other fluid following the bleeding. Any animal designated as having survived the procedure was utilized for further experimentation at a later date.

TABLE I

The Survival of Animals Subjected to a Rapid Hemorrhage Equivalent to Four Per Cent of the Body Weight

Dog weight (kg)	Total hemorrhage (ml)	Duration of bleeding (min)	Survival*
17.5	700	10	yes
18.2	720	10	yes
23.0	910	24	47 min
27.4	1090	9	yes
17.3	692	14	sacrificed
19.4	800	19	39 min
12.6	500	9	yes
28.7	1148	19	yes
21.2	848	15	yes
14.0	560	14	yes

* Animal was available for further experimentation two months later.

The hemodynamic variations observed following a rapid critical hemorrhage are presented in Table II. Mean arterial pressure fell 92 mm Hg from a control value of 127 mm Hg to a mean value of 35 mm Hg. Indication of recovery was evident by the gradual return of systemic pressure toward control with a mean value of 75 mm Hg being reached in one hour. Mean pulmonary arterial pressure dropped 5.2 mm Hg and rose 2.3 mm by the final reading. Very little change occurred in mean coronary sinus pressure. A significant increase in heart rate was found one hour post hemorrhage. Cardiac output was diminished markedly immediately after hemorrhage—from 2.6 *l* to 0.2 *l*/min. This fall in cardiac output is a

TABLE II

Variations in Cardiovascular Functions as a Consequence of Acute Rapid Hemorrhage

Item	Control		Change from control after hemorrhage			
			Immediate		1 hour	
	Mean	S.D.	Mean	S.E.M	Mean	S.E.M
Mean arterial pressure, mm Hg	127	20.2	−92	5.1	−52	9.1
Mean pulmonary arterial pressure, mm Hg	8.7	4.09	− 5.2	1.38	− 2.9	1.47
Mean coronary sinus pressure, mm Hg	3.3	3.60	+ 0.7	1.39	+ 0.04	1.20
Heart rate, beats/min	150	9.4	+ 0.0	9.3	+33	11.35
Arterial hematocrit, %	44.5	5.33	− 1.1	1.28	− 0.6	1.54
Pulmonary arterial hematocrit, %	42.8	5.03	+ 0.01	1.10	− 0.4	0.85
Coronary sinus hematocrit, %	45.8	6.30	− 1.3	1.11	− 0.3	0.99
Arterial oxygen content, vol.%	17.9	2.04	− 1.38	0.45	− 0.6	0.62
A-MV O_2 difference, vol.%	4.75	1.39	+ 4.52	1.50	+ 4.92	1.55
Cardiac output, *l*/min	2.57	0.82	− 2.38	0.35	− 1.49	0.56
Coronary blood flow, ml/100 g left vent./min	85	19.4	−37	13.2	−37	10.4
Coronary blood flow, ml/left vent./min	54	20.5	−26	10.8	−27	9.9
Coronary vascular resistance	1.51	0.37	− 0.77	0.29	+0 .03	0.32
Coronary sinus oxygen content, vol.%	4.59	1.85	− 2.90	0.70	− 2.52	1.09
Oxygen consumption of left ventricle, ml/min	7.1	4.13	− 2.9	1.36	− 2.7	1.68
Aerobic energy uptake of left ventricle, kgM/min	14.3	8.22	− 5.7	2.70	− 5.3	2.97
Work of left ventricle, kgM/min	4.64	1.40	− 3.84	0.53	− 2.76	1.41
Mechanical efficiency L.V., %	23	10.4	−19	1.0	− 3.3	1.7

reflection of both a reduced systemic oxygen consumption and a doubling of the mixed arteriovenous oxygen difference. An hour after bleeding the cardiac output had risen to approximately 42 per cent of control values. The arterial oxygen content did not significantly change throughout the experiment. Hematocrit values also remained constant. Coronary blood flow in ml/100 g left ventricle/min fell from a control value of 85 to 48 immediately after hemorrhage and remained at this level at the final determination. Coronary sinus oxygen content decreased 1.69 volumes % from a control value of 4.59 remaining at this latter level during the recovery period. The left ventricular oxygen consumption was 7.1 ml/min during the control period and this also decreased following hemorrhage to a value of 4.2 ml/min. Left ventricular work fell significantly from 4.6 kgM/min to 0.80 kgM/min. Both left ventricular oxygen consumption and work were below control levels although not statistically significantly so an hour after hemorrhage. The mechanical efficiency was 23 per cent during the control period but fell to 4 per cent immediately after hemorrhage. The level of efficiency had returned to 20 per cent after the one hour recovery period. Coronary vascular resistance decreased from 1.51 to 0.74 immediately after hemorrhage but had attained control levels an hour later.

Discussion

Mortality in this series was similar to that previously reported.[8] Reynell *et al.*[9] also employed an acute bleeding procedure, although less severe than the present series, reinfused the animals, and observed a comparable recovery. It was noted that no animal died after termination of the experiment. Apparently, compensation for the loss of blood began immediately and, once adequately begun, continued to a satisfactory conclusion. In these experiments, therefore, two phases of the animal's response to massive blood loss could be evaluated. The sample immediately following the hemorrhage determined the state of the animal consequent to the sudden large blood loss. The sample drawn one hour later, taken during the animal's adjustment to a diminished blood volume, indicated the efficiency of the compensatory processes.

Immediately following hemorrhage, cardiac ischemia was apparently present as evidenced by the decreased coronary blood flow and coronary vascular resistance. The reduced oxygen consumption, work, and mechanical efficiency of the left ventricle are further indications of the lowered metabolic level in the cardiac tissue. However, 14 per cent of the total cardiac output was delivered into the left ventricular muscular mass during this period in contrast with 2 per cent during the control and all but two of the animals exhibited an increased arterio-coronary sinus oxygen difference indicating the effective removal of additional oxygen from the available flow. In contradiction to the conclusions made by Edwards *et al.*[2] the heart is capable of compensating for the reduced coronary flow in shock states by increasing the myocardial extraction of oxygen. The marked drop in coronary vascular resistance at this time when a similarly pronounced rise of total vascular resistance was present suggests that the coronary blood flow may be somewhat greater than would be expected on the basis of other simultaneously occurring events. It may even be postulated that it was at least adequate for the conditions present, and it further implies that a decrease in coronary blood flow may be a poor index for suggesting cardiac failure in hemorrhagic shock and indicating a state of inadequacy leading to the production of metabolic and hemodynamic disturbances.

This possibility is strengthened by the data obtained an hour later. The mean arterial pressure had risen appreciably, although still far from control levels. The coronary blood flow, ventricular work and oxygen consumption remained at their low levels while mechanical efficiency was greatly improved. Since these events occurred with a concomitant increase in cardiac rate, the return of coronary vascular resistance to normal levels while the total peripheral resistance was still returning toward control indicated the importance of mechanical cardiac compression effects in maintenance of coronary vascular resistance. The cardiac output had increased to 40 per

cent of control and now again 2 per cent of the total output was being delivered to the left ventricular tissues. However, the myocardium was extracting less total oxygen from the blood supply but more oxygen from each ml of blood perfusing the left ventricle.

Opdyke and Foreman[1] suggested that the reduction of coronary blood flow in hemorrhagic shock was due to a decrease in pressure head due to a decline in mean aortic pressure. In these studies on acute hemorrhage no such precise relationship could be demonstrated. The fall in coronary flow was approximately the same with marked differences in blood pressure reduction. These data suggest the intervention of other factors not clearly recognized at the moment concerned with regulation of coronary blood flow. However, the differences between these data and those of other observers could be related to the fact that they were studying irreversible shock while in these experiments reversible hemorrhagic shock was being investigated. The significance of the relative constancy of all changes in myocardial dynamics from the initial response to the hemorrhage to the period where only cardiac output and vascular resistances are returning toward control levels cannot be determined by the available data. However, it suggests that evaluation of other properties of the myocardium during this period might prove most enlightening in providing an understanding of the means by which the adjustments to hemorrhage are being made.

Summary

The rapid removal of a large volume of blood from an animal leads to a lowered arterial pressure, cardiac output, coronary blood flow and an increased extraction of oxygen by the myocardium. These responses are not greatly modified during the first hour of adjustment to this stress. The major corrective responses observable at this time were increases in cardiac output and coronary vascular resistance accompanied by a decrease in total peripheral vascular resistance. The coronary blood flow had not returned to its normal value although the fraction of the cardiac output delivered to the left ventricular muscular mass was essentially normal.

Acknowledgments

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Report on Therapy

Oral Protoveratrine in the Treatment of Hypertension*

MARIANO M. ALIMURUNG, M.D., F.A.C.C. *and* MARIA Z. GRAJO, M.D

Manila, Philippines

PROTOVERATRINE, first isolated by Salzberger[1] in 1890, is a purified derivative of veratrum album from the European or white flowered veratrum plant. The pharmacologic studies of Krayer and associates[2–4] have shown that protoveratrine is superior to the alkaloids from veratrum viride which is found in North America.

Although veratrum viride had been used as far back as 1859 to control the convulsions of eclampsia,[5] it was Mangiagalli[6] in 1908 who first observed a fall in the blood pressure of patients with toxemia of pregnancy when given veratrum. Further observations on blood pressure changes were reported by Collins[7] in 1915. MacNider[8] in 1925 stated that eclamptic convulsions could be prevented by veratrum whenever the pulse rate was slowed to 65 per min or less.

Interest in the clinical usefulness of protoveratrine in hypertension was recently reviewed principally as the result of the studies of Meilman and Krayer.[9] In 1952, Hoobler and associates[10] reported very impressive results following the oral administration of protoveratrine in hypertensive patients. The recent report of Currens, Myers, and White[11] in 1953 on a total of 100 hypertensive patients has given further support to the experience of Hoobler *et al.* These authors concluded that the administration of protoveratrine is a reasonably safe method of drug treatment of hypertensive vascular disease. Their detailed observations on 27 patients with severe hypertensive disease treated with protoveratrine for periods of six months to three years yielded very encouraging results with evidence of both objective and subjective improvement.

The purpose of this report is to present our experience with oral protoveratrine in 30 patients with hypertensive vascular disease. It must be admitted that a final evaluation of any treatment for hypertension cannot be made unless the study is based on a large number of patients observed for many years. This is easily understood when one considers the natural history of hypertensive vascular disease with its characteristic variable course. Hence, the experience herein described is not intended to serve as a final evaluation of protoveratrine in hypertension. It is hoped, however, that these observations may contribute a small share to those from other centers, this time as the first experiences from the Philippines on oral protoveratrine in hypertension.

MATERIAL AND METHOD OF STUDY

This study was started on February 17, 1953. A total of 30 patients were observed in the Charity Services of the Santo Tomas University Hospital, the V. Luna General Hospital, and the private service of one of us (M.M.A.). This investigation was limited to the oral use of protoveratrine in an effort to determine the therapeutic efficacy of its oral use, from the point of view of its potency and its practicability for long-term use.

* From the Department of Medicine and Cardiovascular Section, Faculty of Medicine, University of Santo Tomas and the Santo Tomas University Hospital, Manila.

TABLE I
General Data of Cases

Total number of cases	30
Age range	35–74 years
Sex distribution	17 males
	13 females
Etiologic diagnosis of hypertension	
1. Essential hypertension	25
a. Benign	21
b. Malignant	4
2. Chronic glomerulonephritis	4
3. Pheochromocytoma	1
Other clinical features	
1. Acute pulmonary edema (left ventricular failure)	3
2. Azotemia	6
3. Cerebrovascular accident	3
a. Hemorrhage	2
b. Thrombosis	1

Table I gives the general clinical data in these patients. There was a more or less equal number of male and female patients. No particular age group was chosen, notwithstanding the possibility that in the older patients a less favorable response might be encountered. This was purposely done in order to test the hypotensive efficacy of the drug.

In 25 of the patients, no etiologic cause of the hypertension could be discovered; hence, they were classified as cases of essential hypertension. Of these, 21 were considered benign and four presented signs and symptoms of malignant

TABLE II
Observations on the Blood Pressure

Patient	Before treatment	Maximum drop	Average drop
1. S. G.	200–270	120	150
	110–140	70	90
2. A. M.	144–200	130	150
	74–116	80	90
3. F. S.	180–200	146	170
	120–140	92	100
4. V. E.	190–260	130	140
	95–150	35	50
5. E. M.	230–300	165	180
	140–190	88	100
6. E. U.	240–290	130	170
	120–140	80	90

TABLE II *Continued*
Observations on the Blood Pressure

Patient	Before treatment	Maximum drop	Average drop
7. P. V.	196–240	155	160
	124–150	98	105
8. E. I.	244–270	120	150
	130–150	90	100
9. M. L.	230–260	112	160
	130–150	90	100
10. R. B.	260	140	180
	120	76	90
11. J. R.	200	160	162
	110–140	90	100
12. R. V.	192	174	160
	116	98	100
13. L. J.	246	140	146
	130	80	80
14. I. M.	240	128	180
	140	70	100
15. E. T.	198	152	168
	100	80	90
16. R. B.	218	110	160
	120	70	92
17. H. P.	195	140	170
	120	100	100
18. M. R.	230	138	160
	120	70	96
19. C. T.	260	190	210
	120	95	110
20. M. K.	224–242	158	180
	142–150	118	120
21. J. B.	240	88	110
	130	40	70
22. C. A.	200–220	138	160
	110–140	94	100
23. A. L.	220	136	150
	130	60	70
24. S. O.	186–200	110	160
	90–108	60	70
25. G. E.	184	120	140
	84	60	70
26. E. M.	210	146	150
	110	98	100
27. D. I.	260	130	154
	180	88	98
28. P. D.	230	144	150
	140	90	100
29. F. G.	210	130	150
	130	88	98
30. H. G.	220	—	—
	160		

hypertension. In the remaining five patients, the hypertension was related to a specific disease; namely, chronic glomerulonephritis in four and pheochromocytoma, discovered at autopsy, in one.

Complications consisted of azotemia in six, pulmonary edema secondary to left ventricular failure in three, and cerebrovascular accident in three. The latter consisted of cerebral thrombosis in one and hemorrhage in two. In one instance, case 3, there was coexisting pregnancy and pre-eclampsia.

The basic criterion followed in the selection of cases was a persistent and moderate to severe degree of hypertension. In Table II it can be seen that the pre-treatment blood pressure levels were, as a rule, significantly over 200 mm systolic and 110–120 mm diastolic.

Observations on the blood pressure and cardiac rate were made at hourly intervals and in a good number of the cases at half-hourly intervals. This was possible because practically all of these patients were started on protoveratrine in the hospital. Routine studies included the electrocardiogram, roentgenograms, funduscopy, and various laboratory examinations such as urinalysis, blood counts, blood nonprotein nitrogen, urea nitrogen, creatinine, and carbon dioxide combining power especially in the patients with renal insufficiency. The diet was moderately restricted in sodium content. As far as possible, no other medication was given, except for oxygen and sedatives when the condition demanded their use.

In the first ten cases, the dosage schedule followed was that recommended by Hoobler and associates; namely, a relatively large dose at 8 a.m., 0.5–0.75 mg, followed by two reinforcing smaller doses, 0.2 mg at 10 a.m. and 1 p.m. The exact amount for these doses was subsequently varied according to the hypotensor response obtained. In the remaining cases, following the plan of Currens, Myers, and White,[11] the drug was given every eight hours in gradually increasing dose until the desired response was obtained. In one case, the maximum dose reached 1.5 mg every six hours.

In the three cases with acute pulmonary edema secondary to left ventricular failure, protoveratrine was the only hypotensor given. No digitalis nor morphine was administered.

TABLE III
Observations on the Cardiac Rate

Patient	Before treatment	Maximum drop	Average drop
1. S. G.	100–122	70	85
2. A. M.	80	38	70
3. F. S.	120	85	90
4. V. E.	117–120	86	88
5. E. M.	88– 96	56	75
6. E. U.	80– 95	52	65
7. P. V.	84–104	70	78
8. E. I.	82	60	70
9. M. L.	100–120	80	85
10. R. B.	126–139	95	105
11. J. R.	75	58	70
12. R. V.	108	90	98
13. L. J.	90–100	65	70
14. I. M.	80	43	70
15. E. T.	80	70	76
16. R. B.	65	43	60
17. H. P.	113	80	95
18. M. R.	80	68	72
19. C. T.	52	45	50
20. M. K.	92	70	84
21. J. B.	128	62	84
22. C. A.	72	54	58
23. A. L.	100	52	65
24. S. O.	56	50	52
25. G. E.	90	60	62
26. E. M.	80	70	72
27. D. I.	120	106	115
28. P. D.	82	67	72
29. F. G.	92	54	65
30. H. G.	90	—	—

Results

Tables II and III present the observations on the blood pressure and cardiac rate. The detailed report on the first ten cases in the series has already been published previously.[12]

In Table II it can be seen that in all, except one, there was a significant and satisfactory drop of the blood pressure. The only case in which no observation on the blood pressure was obtained was in case 30, who could not tolerate the drug. This was a 27-year-old male patient in renal failure due to chronic glomerulonephritis. Already nauseated and vomiting, he apparently felt worse with protoveratrine.

In the 29 cases wherein the drug was tolerated, the maximum drop in pressure varied. In case 21, it came down as low as 88/40. In 21 of the cases, the systolic level dropped to below 150 mm whereas the diastolic pressure came down 90 mm in 21 instances and in only one did it fail to drop to less than 100 mm.

The average drop was of special interest because of its practical implications in the possible long-term use of the drug. That the average blood pressure following oral protoveratrine comes to a fairly reasonable level, often to normal, is also seen in Table II.

Figures 1 and 2 are illustrations of the blood pressure curve in five of the cases. Figure 1 is of case 6 showing the behavior of the blood pressure in six consecutive days. Figure 2 shows the same daily observations in four different patients. These curves indicate that the response to oral protoveratrine is fairly satisfactory, consistent, predictable and with sufficient degree of relation to the amount of drug administered. These charts also suggest not only a drug-response relation but also a time relation between the administration of the drug and the maximum as well as total duration of response. The maximal response seems to appear at about the second hour following the oral dose and gradually wanes in approximately eight hours.

The slowing of the cardiac rate is one interesting observation reported by Krayer and coworkers[3] as well as by subsequent workers.[10,11] Our own experience corroborates this protoveratrine effect as shown in Table III. Again excepting case 30, in all the remaining 29 cases, the heart rate slowed down significantly. The maximal slowing was to 50 per min or less in five cases, whereas the average pulse rate at the time of the average drop of the blood pressure did not go over 100 per min, except in two instances. In case 2 the pulse rate

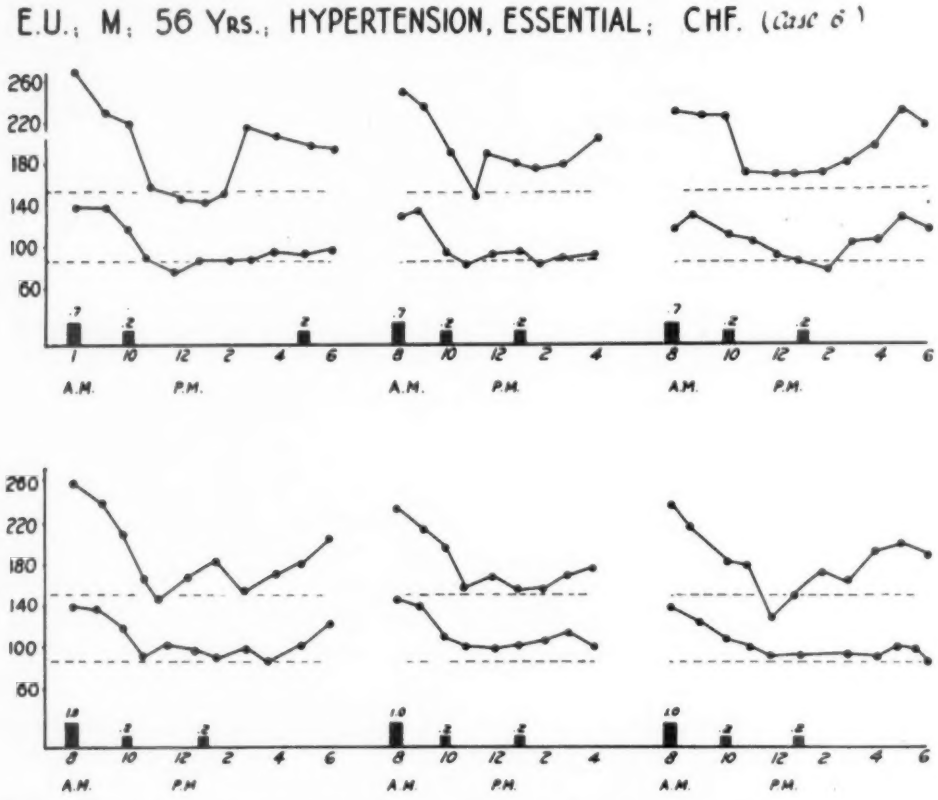

Fig. 1. Daily observations on the blood pressure during six consecutive days in case 6. Note close similarity of daily responses to the drug.

slowed to 38 per min but no untoward effect attributable to the bradycardia was noticed; indeed this patient tolerated the drug very well. These bradycardic responses paralleled the drops in blood pressure indicating that the bradycardia was also a direct effect of the drug.

Reduction in blood pressure and perhaps also the bradycardic effect (as suggested by Hoobler *et al.*) could provide significant relief for the failing left ventricle when protoveratrine of protoveratine was reduced, the blood pressure rose again and the patient eventually succumbed. Although protoveratrine failed to produce a complete therapeutic success in this case, the relief of cardiorespiratory difficulty coinciding with the hypotensive and bradycardic response served as an inspiring experience.

Cases 21 and 23 were similarly admitted in acute pulmonary edema due to severe hypertension and left ventricular failure. In both

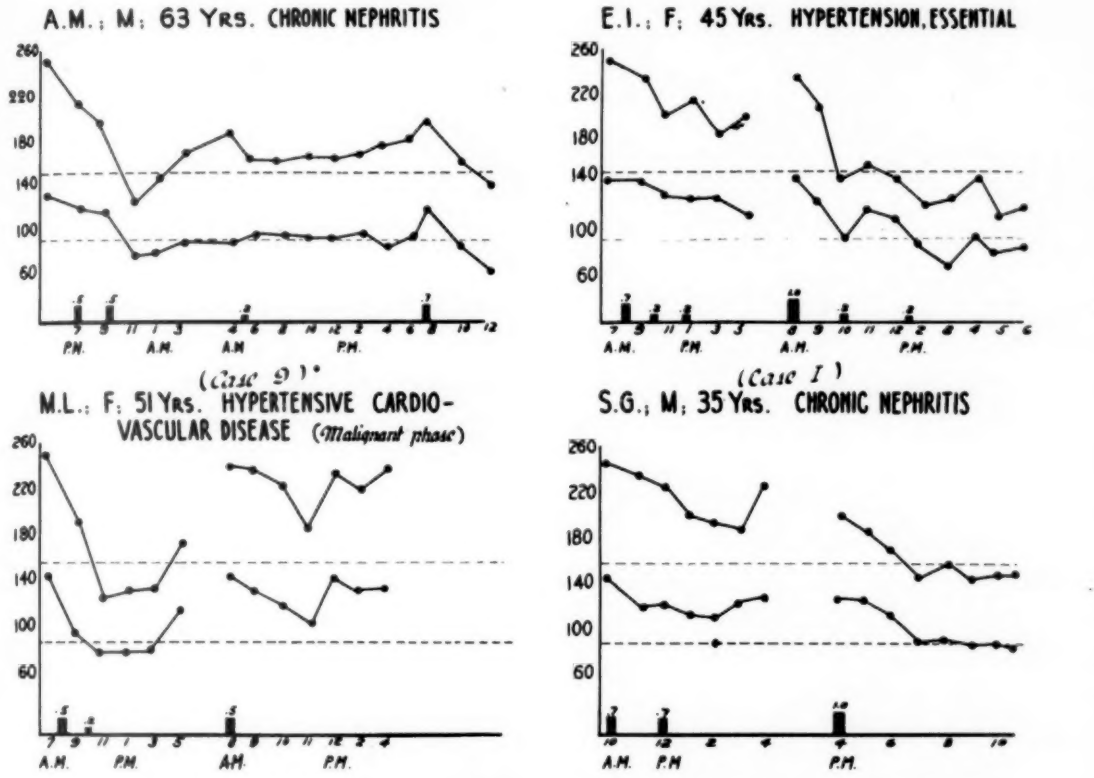

Fig. 2. Observations on the blood pressure in four cases (cases 2, 8, 9, and 1). A fairly satisfactory correlation between the amount of the drug and the drop of blood pressure is shown.

is administered. Cases 16, 21, and 23 were of special interest in this regard. These were patients with severe hypertensive cardiovascular disease and left ventricular failure with pulmonary edema. Figure 3 shows the clinical course in case 16. It can be seen that there was a satisfactory response to the initial protoveratrine therapy. Unfortunately, the patient was nauseated and vomited easily. This was probably primarily due to the renal failure and aggravated by protoveratrine. When the dose instances, there was a satisfactory drop of blood pressure and a significant slowing of the heart rate. Even more impressive was the dramatic relief of the pulmonary edema. The morning following their admission, these patients were sitting comfortably in bed, dyspnea was gone, the lungs were clear, the gallop rhythm had disappeared. In case 21 (Fig. 4), as the protoveratrine was continued, the blood pressure continued to drop and the patient vomited and became stuporous. Upon discontinuance

of the drug, these side-effects disappeared and the blood pressure rose gradually to more satisfactory levels. Subsequently, as long as the blood pressure was maintained at approximately 160/90 no pulmonary edema occurred. However, on two other occasions when protoveratrine has been discontinued, the patient had recurrences of this acute crisis; in both episodes, protoveratrine gave the same dramatic relief.

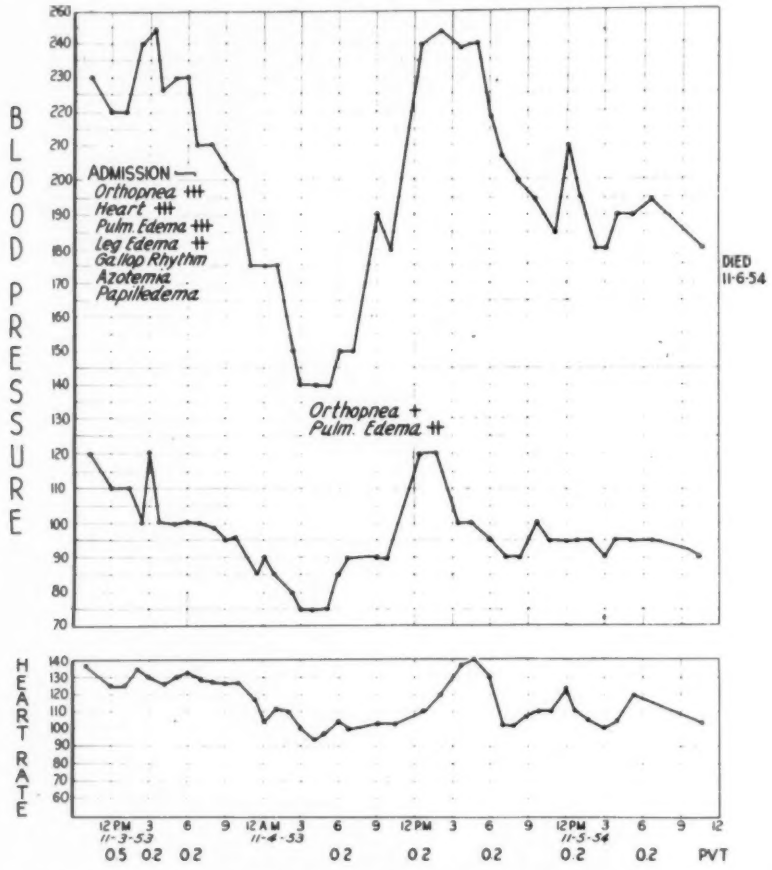

Fig. 3. Observations on the clinical course, blood pressure, heart rate and dose of drug in case 16, a 49-year-old male with malignant hypertension and combined left and right ventricular failure.

Relief of headache was observed in three cases. Although it is difficult to evaluate the exact cause of headache in hypertension, it is of interest to note that the relief of headache coincided with the drop in blood pressure.

In seven patients, vomiting occurred. Of these, however, five were patients with azotemia, and two were cases of cerebral hemorrhage. How much of the vomiting was caused by protoveratrine and/or by the azotemia or cerebral apoplexy cannot be ascertained. Stupor occurred in one case and mental disturbance, in the form of restlessness and incoherence, developed in two patients. These psychic phenomena were transitory and short-lasting, subsiding spontaneously following withdrawal or diminution of the dose of protoveratrine. One patient complained of chest warmth and mild tightness about an hour following protoveratrine, at the time when his blood pressure had dropped from 190 to 110 systolic. This complaint was also transitory and disappeared spontaneously.

Although not all of these patients could be followed for a long period of time, in those who continued the drug it was observed that the blood pressure could be maintained satisfac-

torily at reasonable levels with a schedule of three eight-hourly doses. In some instances, nausea would develop after seven to ten days of continuous therapy, especially when the doses exceeded 0.5 mg three times a day. Case 20 was one such patient who developed nausea when he was on 0.75 mg three times a day. This problem was solved by diminishing the dose to 0.5 mg and giving complementary treatment with rauwolfia serpentina.

There were four patients who died, two from renal failure and two from cerebral hemorrhage. At the time these patients were admitted, they were already in a serious state and, therefore, we felt that protoveratrine could not have contributed to an aggravation of their primary illness.

The period of observation in these patients was a variable one chiefly because of the fact that most of them were private patients and, therefore, could not be examined as frequently as would be desirable in a very critical study. On the average, the period of observation in this study was anywhere from six months to a year since the start of protoveratrine therapy.

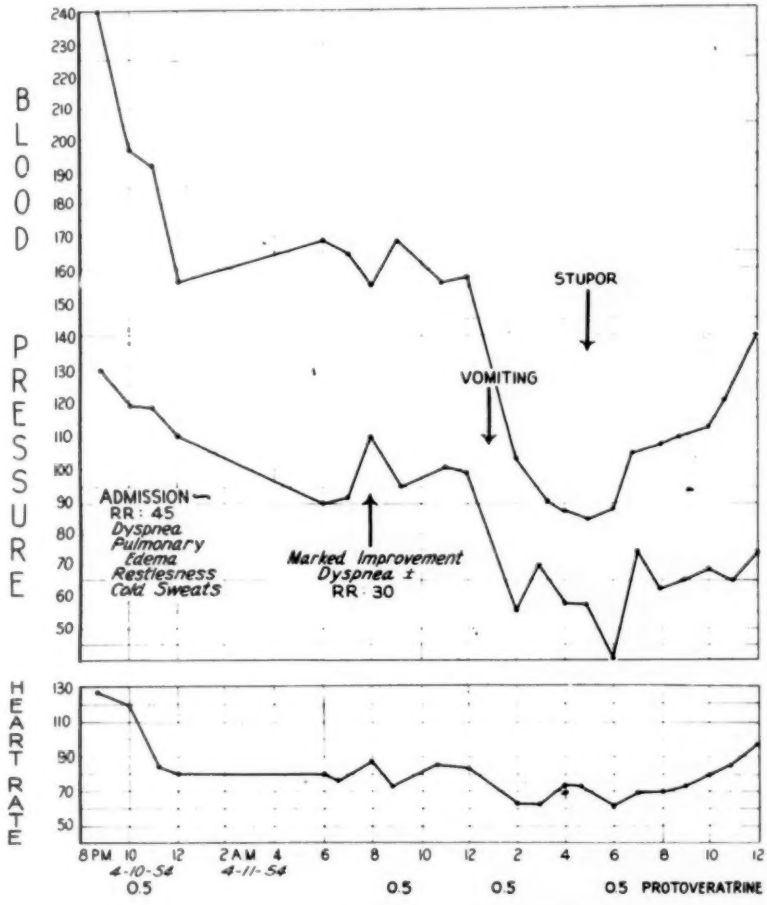

Fig. 4. Observations in case 21, a 68-year-old hypertensive female with acute pulmonary edema due to left ventricular failure.

In two of the cases, the drug has been continuously taken without interruption up to the present time, almost four years since they were started on it, and has never produced any significant untoward effect. If nausea at all occurred, it was when they reached a dose of 0.75 mg three times a day. To date, they are on 0.5 mg every eight hours and the blood pressure averages 150/88 whereas prior to proto-

veratrine therapy it always registered over 200 systolic and 110 diastolic.

Discussion

These observations confirm those reported by Hoobler *et al.*,[10,13,14] Meilman and Krayer,[19] and Currens, Myers, and White.[11] As Hoobler found, all forms of hypertension appear to respond to protoveratrine. While not a curative form of treatment, oral protoveratrine appears to have certain advantages over various other oral hypotensors. Certainly it is a very potent hypotensive agent. In a carefully adjusted dosage schedule, protoveratrine can reduce and maintain the blood pressure to reasonable if not normal levels for a sufficient time and with predictability and consistency. Such control of the blood pressure, while temporary and dependent on the drug, is of a magnitude and duration adequate to afford significant subjective and objective relief.

Hoobler's group[13,14] has shown that protoveratrine administration is accompanied by a decline in resistance to blood flow in the renal and peripheral vascular beds. Meilman[15] admits the possibility that further nonprotein nitrogen retention might occur if the blood pressure is lowered rather rapidly and markedly. On the other hand, Hoobler[16] has found neither improvement nor worsening of the renal function in his cases. In general, it might be stated that in patients with severe renal insufficiency, protoveratrine should be given cautiously and only when clearly indicated by other disturbing symptoms brought about by the severity of the hypertension.

Other Cardiac Effects: Recent work with cardiac catheterization has shown that protoveratrine produces a fall in systemic blood pressure both by causing vasodilatation and by decreasing cardiac output, thus resulting in a reduction of the work of the left ventricle.[17,18] The significant slowing of the heart rate is an interesting consistent effect in this regard. The relief of pulmonary edema in patients with left ventricular failure is also a very impressive result. This can be explained by the finding of a fall in pulmonary artery and "pulmonary capillary" pressures following protoveratrine, as reported by Myers *et al.*[17] This is probably one advantage of protoveratrine over various other hypotensive agents in the relief of hypertensive heart failure with severe pulmonary edema.

The production of chest warmth and even discomfort is also worthy of note. Meilman attributes this to a reflex action of the drug rather than to true angina. In patients with hypertension and angina, given protoveratrine deliberately, he failed to produce any discomfort due to angina from the drug.[19] In the series of Currens and associates this sensation was felt by many patients at about 30 to 60 min after the ingestion of the drug. Indeed this served as a good indicator that the drug was reducing the blood pressure. Nevertheless, the possibility of inducing true angina by a sudden and marked drop in blood pressure cannot be completely overlooked.

Gastric upset and vomiting constitute the most frequent side-effects of protoveratrine. This is likely to happen more easily in patients prone to develop vomiting, as in our cases with renal insufficiency and cerebral hemorrhage. There is, of course, the occasional patient who cannot simply tolerate the drug at all.

Arrhythmias: In this series we did not run into any serious difficulties with regard to the production of arrhythmias as reported by various observers. In one patient who received inadvertently an overdose of protoveratrine, Black and Lyons[21] observed the appearance of atrioventricular dissociation. Six hypertensive patients studied by Margolin, Levine, and Merrill[22] likewise developed various forms of cardiac arrhythmia while receiving protoveratrine. These arrhythmias consisted of sinus bradycardia, sinus arrest, wandering pacemaker, first degree atrioventricular block, and partial and complete atrioventricular dissociation. In all of these instances the disturbed cardiac mechanism reverted to normal sinus rhythm with time or with the administration of atropine. The arrhythmias reported were believed to be due to excessive vagal stimulation by protoveratrine. In the latter series, it must be further mentioned that digitalis was being administered in four of the six cases studied. This may or may not have had a bearing on the

production of arrhythmia either as an exclusive digitalis ill-effect or as the result of a synergistic action of the two drugs combined. In our own cases, while cardiac slowing was frequently observed, we did not encounter, in those with electrocardiographic control during the bradycardia, any more serious arrhythmia than sinus bradycardia. In view of the reported experience of others, however, the possibility of more serious types of arrhythmia must be borne in mind, especially in cases where the drug is given parenterally, in large doses, and for a prolonged period of time. This fact also stresses the importance of controlling carefully the dose of the drug given and of observing the patients closely.

Dosage Schedule: The question of dosage schedule appears to vary from patient to patient. Hoobler's schedule gives the maximum hypotensive effect during the 8 to 12 hours of the day in which the patient is likely to have greatest activity and probably the highest blood pressure. There is no attempt to continue treatment during the last 12 hours of each 24-hour period. Freedom from side-effects, chiefly the emetic action, is the special advantage of this schedule, as the cumulative effect of the drug is diminished. It is therefore possible that at the time when the blood pressure is not under control, hypertensive vascular crisis may still occur. One of our cases developed fatal cerebral hemorrhage at about 4 o'clock in the morning, when he was not under treatment according to the Hoobler schedule.

The plan recommended by Currens *et al.* appears, therefore, more adequately protective as far as attempting to keep the blood pressure more uniformly controlled during the entire day. The more frequent occurrence of side-effects in this plan may be true, although Currens and associates did not meet this difficulty frequently in their cases. Our experience further shows that if side-effects occur a reduction of the dose of protoveratrine together with a complimentary treatment with rauwolfia serpentina generally avoids nausea and vomiting while maintaining the blood pressure at comfortable levels.

There is therefore sufficient evidence that oral protoveratrine is an effective and practical form of drug treatment in hypertensive patients, particularly those with symptoms or syndromes due to severe hypertension. This is especially remarkable in patients with acute pulmonary edema due to left ventricular failure, where protoveratrine may be practically life-saving.[20]

It must be emphasized that oral protoveratrine cannot be a cure of hypertension and that it must be administered with caution and intelligent supervision, especially at the start of treatment. The effective dose must be determined by trial and error, until the adequate results are obtained. Adjustment of dosage can be a delicate task so as to obtain the beneficial effects without inducing side-effects either when given alone or with rauwolfia serpentina.

The combination of rauwolfia and protoveratrine has also been found advantageous and effective, as reported by the independent work of Smith *et al.*[23] in 1955 and by Gibbons and associates[24] in 1956. In said studies, it was observed that these drugs exerted a corrective effect upon each other's possible undesirable side-effects. Further, the dose needed of each was significantly lower than when either one was used separately.

Protoveratrine A and B: In a more recent study, Winer[25] has pointed out that protoveratrine is actually not a single alkaloid; rather, it is a mixture of two alkaloids, protoveratrine A and protoveratrine B. He also presented suggestive evidence that there may be significant differences in activity between these two component alkaloids of protoveratrine. Wyss and Spuhler[26] reported similar observations on the quantitative differences between protoveratrine A and protoveratrine B given orally. These observations are somewhat different from those previously reported by Abreu *et al.*[27] from the pharmacologic point of view and by Meilman[28] from the clinical side. Our own experience cannot clarify this varying experience and therefore it would appear that further studies on this matter seem indicated. Nonetheless, our favorable results indicate that protoveratrine is indeed an effective oral hypotensive agent which can be administered safely even for a long course of treatment as long as dosage is carefully supervised and the undesirable

effects promptly detected and managed. The latter can actually be minimized, if not adequately prevented, when the drug is given in combination with rauwolfia.

Summary

Protoveratrine was administered orally in 30 hyptertensive patients. These patients were unselected in so far as their age and the probable cause of the hyptertension was concerned. Twenty-five were considered as having essential hypertension, four, chronic glomerulonephritis and one, pheochromocytoma.

In 29 patients who tolerated the drug, a significant reduction of the blood pressure to reasonable, often normal, levels was obtained. The drop in blood pressure was observed to be fairly consistent and closely related to the drug dosage.

The cardiopulmonary effects consisted of slowing of heart rate and a dramatic relief of acute pulmonary edema. The latter, as suggested by others, may be due to the drop in pulmonary artery and "pulmonary capillary" pressures.

The most frequent side-effects were nausea and vomiting, especially in patients prone to develop these manifestations as in those with renal insufficiency or cerebrovascular accident. Psychic disturbances were observed in two cases. Substernal warmth or mild tightness occurred in one case. This is probably a reflex action of the drug, although the possibility of induced angina is not to be overlooked especially when the blood pressure drops rapidly.

Oral protoveratrine, administered in the dosage schedules mentioned, appears to be a useful, potent and safe drug treatment of hypertension and hypertensive heart disease.

Acknowledgment

The authors express their gratitude to Eli Lilly and Company for the generous supply of protoveratrine (Provell malleate tablets) for this study, prior to the product becoming available for general use in the Philippines.

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Case Reports

Report of an Unusually Large Ventricular Aneurysm*

MORRIS W. DEXTER, M.D., ALFRED H. LAWTON, M.D., *and* ARTHUR H. RAYNOLDS, M.D.

Bay Pines, Florida

VENTRICULAR aneurysms are rather frequent complications of myocardial infarction, with an incidence ranging from 10 to 20 per cent in large series.[1,2] They are frequently discovered during life by means of chest x-rays or fluoroscopy. The aneurysm appears as an abnormal bulge in the cardiac silhouette and often exhibits paradoxic pulsations.[3] Physical findings may suggest ventricular aneurysm by a weak diffuse apical impulse and muffled heart tones, but these are not as definitive as roentgenologic examination. Occasionally such aneurysms may reach immense dimensions, as in a case reported by Shennan and Niven,[4] in which the internal diameter of the sac was 16 cm. At the time of their writing this was the largest reported ventricular aneurysm. In the case report which follows, a ventricular aneurysm even larger (over 18 cm) than that of Shennan and Niven is described.

CASE HISTORY

This 43-year-old white male was first admitted to Bay Pines VA Center two days following a cramping, anterior chest pain which radiated down both arms. The pain was relieved by an injection of a narcotic. The patient gave a past history of bronchial asthma for which he had been discharged from the Navy, and a recent accident, the exact date of which had not been determined, in which he suffered fracture of some left ribs.

Physical Examination: The patient was a well developed and well nourished 43-year-old, grey-haired white male, who appeared much older than his chronologic age. The blood pressure was 135/90 and pulse 102. The heart sounds were of good quality. There were no murmurs or signs of failure. Remainder of physical examination was negative.

Laboratory and X-ray Findings: Red blood count 4,920,000; hemoglobin 94%, hematocrit 49; WBC 10,000; BUN 11.5; cholesterol 320; urinalysis negative; sedimentation rate 19; Kahn negative. ECG showed recent anterior wall infarction.

Hospital Course: The clinical diagnosis was acute coronary occlusion with myocardial infarction. The patient was placed at bed rest and given anticoagulant treatment, including heparin and dicumarol. He improved clinically and after five months was discharged to the domiciliary unit. At time of discharge, his only complaint was occasional angina.

Second Admission: Approximately one year later the patient was admitted for a second time because of chest pain and dyspnea. Physical examination was negative except for wheezing and moist rales in the chest. Blood pressure 104/80; heart rate 80, gallop rhythm; no edema.

Laboratory and X-ray Data: X-ray revealed an aneurysmal bulge along the upper border of the left ventricle. Otherwise, laboratory findings were within normal limits.

Hospital Course: Patient responded well to bed rest, 200 mg sodium diet, digitoxin 0.2 mg daily, nitroglycerin when needed. He was discharged to the domiciliary unit at the end of one month.

Third Admission: The patient was admitted for the third time 18 months later complaining of generalized weakness with weight loss, nausea, intermittent pain in his chest and shoulders for several months. He had gradually developed more dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and slight dependent edema.

Physical examination showed a chronically ill, thin white male who appeared over 60 years of age rather than his actual age of 43. He was too weak to sit up during an examination. Height 5 ft 10 in.; weight 137, temperature 98.6; pulse 100; blood pressure 110/100 bilaterally. There was slight venous engorgement.

* From the Veterans Administration Center, Bay Pines, Florida.

Asthmatic wheezes were heard in both lungs. The heart was enlarged, heart sounds feeble, rhythm regular, occasional extrasystole, no murmurs, A_2 greater than P_2; two plus dependent edema.

Laboratory and X-ray Data: Urine showed 4 plus albumin, otherwise negative. WBC and differential were within normal limits. Red count 4,470,000; hemoglobin 90 per cent; hematocrit 44. Chest x-ray again showed an aneurysmal bulge along the left upper ventricular wall. Lungs showed signs of pulmonary congestion. ECG showed right bundle branch block with possible anterior wall infarction.

Hospital course was characterized by severe generalized weakness and episodes of shock with profuse diaphoresis. During these periods his pulse was imperceptible and blood pressure was unobtainable. Five such episodes occurred during his last hospital period. He often required Demerol® for his chest pain. During his last three weeks he showed evidence of "right-sided failure," which responded poorly to mercuhydrin and low-sodium diet. There was severe epigastric pain, which was partly controlled by Amphogel and Methadon.

At the end of the fifth week he complained of severe left pleuritic pain and on the following day he expectorated some bloody sputum. Pericardial and left pleuritic friction rubs were heard. Because of these evidences of pulmonary infarction, he was placed on anticoagulant therapy with Dicumarol. Nevertheless, his chest pains persisted and he developed a fever which failed to respond to penicillin and streptomycin. His condition deteriorated rapidly despite oxygen and other supportive measures. It should be stressed that even at this stage the most salient symptom complex was that of chronic shock rather than right-sided failure. Edema and hepatomegaly appeared late but were never impressive. Following gradual fall in blood pressure the patient expired 46 days after admission.

Necropsy Revealed:

(1) Aneurysm of left ventricle.

(2) Myocardial infarction, old and recent, right and left, due to coronary thrombosis.

(3) Mural thrombosis, left ventricle.

(4) Pulmonary infarction, left lung, due to embolism.

The aneurysm was an exceedingly thin sac measuring over 18 cm in internal diameter (Fig. 1). It was completely filled with a laminated mural thrombus which, though adherent to the ventricular wall, could be easily separated. Calcification of either the thrombus or the aneurysmal sac was not noted. There was no conspicuous pericardial reaction.

Discussion

Ventricular aneurysms may attain enormous

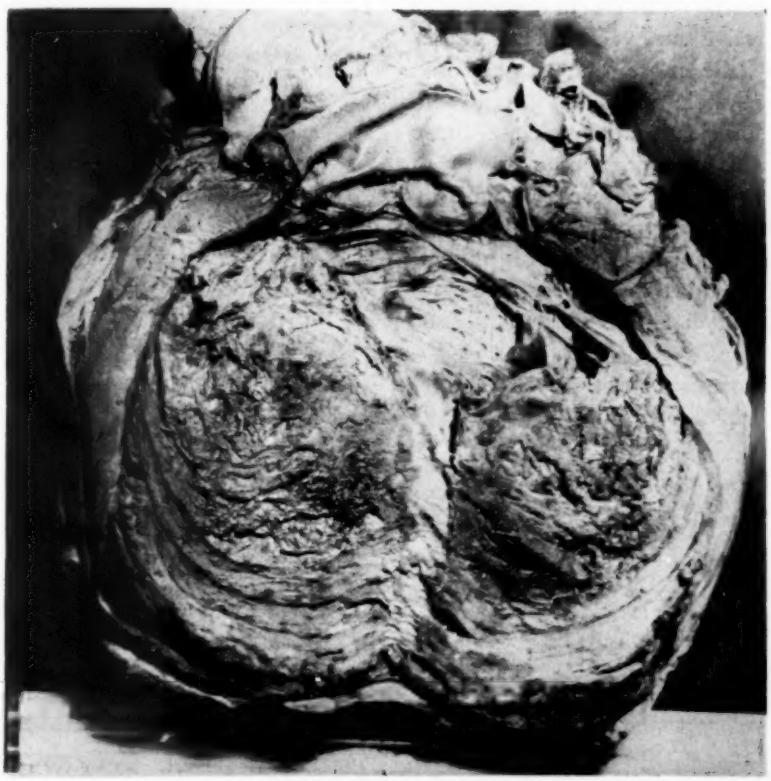

Fig. 1. Sagittal section through left ventricle showing large aneurysmal sac and mural thrombus.

dimensions, as noted above. These are generally passive fibrous sacs with virtually no myocardium. The clinical picture may vary from forward failure due to low volume output to congestive failure. The electrocardiogram is said to show persistent S-T segment elevation[5] but this is not reliable in most instances.[6] Many cases[7] are diagnosed antemortem by physical examination but even more frequently by x-ray or fluoroscopy. X-ray often discloses a characteristic bulge along the left cardiac border where such aneurysms are most common. Posterior or diaphragmatic aneurysms, especially those of small size, may be difficult to demonstrate by ordinary means.[8,9] Fluoroscopy will often show paradoxic movements of the aneurysm during the ventricular cycle. Recently the importance of antemortem diagnosis has been stressed since some may be amenable to surgical treatment.[10,11]

The hemodynamics of ventricular aneurysms constitute an interesting aspect of this problem. Since many aneurysms are larger than the left ventricle even during diastole and since the aneurysms are passive sacs, ventricular contraction should do little more than distend the aneurysm during systole and make virtually no blood available for ejection through the aortic valve. Indeed, this may contribute greatly to the picture of low output failure so frequently observed in patients with ventricular aneurysm. It is our belief that the reason why this patient, and similar patients, are able to survive with large ventricular aneurysms is because the sac is obliterated by the thrombus. In other words, in large ventricular aneurysms the mural thrombus is a lifesaving factor.

Summary

The case of a patient with an exceedingly large ventricular aneurysm has been described. A review of the literature indicates that this may be one of the largest aneurysms yet reported.

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Early Development and Long Duration of Massive Ventricular Aneurysm in Myocardial Infarction

LOUIS H. SIGLER, M.D., F.A.C.C.

New York, New York

ANEURYSM of the heart following myocardial infarction occurs fairly frequently. According to Schlichter and co-workers[1] the recorded frequency in the various autopsy reports in the literature is 5 to 38 per cent. In their own series of 102 cases the figures were 1.8 per cent of general autopsies and 20 per cent of autopsies in myocardial infarction. Likoff and Bailey[2] also estimated that 20 per cent of autopsied cases of myocardial infarction had ventricular aneurysms. These figures, however, do not hold true for the general run of cases of myocardial infarction, as they are based only on autopsy material which represents the most serious and fatal forms of the disease. The average incidence is much lower if we consider the numerous lesser grades of infarction that never come to autopsy.

The incidence of ventricular aneurysms in autopsy cases recently recorded in the literature is far greater than that recorded in the earlier part of the century. Thus, in a general autopsy series of 12,000 patients who died from different diseases, Lucke and Rea[3] in 1921 found only 0.125 per cent of cardiac aneurysms caused by all etiologic factors. The vast increase in the number of cases since that time would suggest that there has been a marked increase in myocardial infarction in the past thirty odd years, inasmuch as most cardiac aneurysms are caused by infarction.

Postinfarction ventricular aneurysms may affect either the apex, the anterior wall, the posterior wall, or the interventricular septum. It rarely occurs in more than one area in the same heart. In a series of 62 cases of cardiac aneurysm reported by Slapak,[4] however, three showed aneurysms in two locations.

The development of a ventricular aneurysm following myocardial infarction usually occurs at variable lengths of time after recovery from the acute infarct. In five cases of postinfarction aneurysm reported by Likoff and Bailey, the aneurysm developed four to twelve months after the infarction. In Schlichter's series, only two cases developed the aneurysm two days after the onset of infarction. The others developed it at variable periods after recovering from the infarction.

CLINICAL FEATURES

Physical Signs: The clinical diagnosis of ventricular aneurysm has in the past been missed in nearly all cases. It was considered mostly a postmortem finding, as was shown in a previous communication.[5] In recent years, however, we have come to diagnose the condition more frequently, owing to the assistance of the x-ray and the electrocardiogram, if specific, and to the fact that we keep the condition more in mind. However, the physical findings lack specificity in most cases. Scherf and Brooks[6] described some murmurs which they observed in three cases. These, however, occur rather infrequently. I have observed a gallop rhythm in an occasional case. In my experience a most frequent early finding is a localized forward thrust felt by the palm of the hand placed over the left lateral precordial region either at the apex or a little above.

This forward thrust is systolic in time and if felt above the apical region is synchronous with the apical systolic retraction. When this finding develops in the course of myocardial infarction, the diagnosis can be made with fair certainty. However, this finding is present only in aneurysm of the anterior wall of the left ventricle. Slapak[7] considers the rapid onset of signs of right heart failure after infarction as a possible diagnostic sign.

Mural Thrombosis and Rupture: A ventricular aneurysm developing in the course of or following myocardial infarction makes the prognosis much more unfavorable than in infarction without aneurysm. The potentiality for intramural thrombi formation and embolization, the greater frequency of congestive failure and the possibility of rupture of the heart at the site of the aneurysm all add to the gravity of the situation. In Schlichter's series, 73 per cent of the patients died within three years and 88 per cent within five years. It is interesting to find, however, that some cases may go on for many years without rupture. In one of the cases of aneurysm I reported,[8] rupture at its site occurred about 10 years after the attack of myocardial infarction which caused the aneurysm. During this interval the patient carried on fairly normal activity at a gainful occupation. Pheres and co-workers[9] reported 40 cases of ventricular aneurysm with no instance of rupture. One of the main reasons for the infrequent incidence of rupture is that reactive inflammatory changes take place in the visceral and parietal pericardium at the site of the aneurysm resulting in massive adhesions, thus binding the area and preventing it from overdistention. If the patient survives long enough, calcification may occur at the site which further protects the area.

Calcification: According to Bogoch and Christopherson[10] calcification is relatively uncommon. It may involve a limited clot inside the aneurysm or the wall of the aneurysmal sac itself. They differentiate a calcified aneurysm roentgenographically from calcified constrictive pericarditis by the finding of a linear shadow in the former which is limited to the left ventricle and is situated within the heart contour. In calcified constrictive pericarditis the calcification is thicker, more irregular, is not restricted to the left ventricle and is outside of the heart contour.

X-ray Findings: The outstanding roentgenologic finding of a ventricular aneurysm, of course, is a localized bulge in the involved area which expands during systole and retracts in diastole, thus forming a paradoxic movement with the adjacent normal portion of the heart. To demonstrate that, a fluoroscopic examination must be made in the anteroposterior, oblique, and lateral positions, depending upon the location of the aneurysm. It must be understood, however, that we cannot always demonstrate the presence of an aneurysm roentgenologically. This is particularly true if it is small or is localized in the posterior wall. It is particularly true where the aneurysm involves the interventricular septum only.

Electrocardiographic Findings: The most important electrocardiographic finding is a persistent elevation of the RS-T segment in the leads overlying the aneurysmal region. There may be also a low voltage or absence of R wave in Lead I and some depression of the S-T segment in Leads II and III, if the aneurysm is localized in the anterior wall of the left ventricle.

The following case is presented because it illustrates most of the points brought out heretofore. It also has some interesting features which are rarely encountered in ventricular aneurysm.

Case Report

The patient is a Hebrew male who first came under my observation in January 1949 at $56\frac{1}{2}$ years of age. He was a tailor by trade. His habits were normal except for the use of tobacco to the extent of 12 cigarettes a day since 15 years of age. He drank no alcoholics and very little coffee. His bowels were always regular and his diet well balanced. His father died at 66 years of age from a stroke and his mother died at 67 years from causes unknown to him. One brother died at 56 years from cancer and three sisters were probably alive in Europe, although he had not heard from them since World War II. He had been married for 35 years and had two sons who were living and well. In his past morbidity

history he claimed to have had pleurisy at 30 years of age for several months, joint pains for a number of years on and off, and "kidney trouble" the nature of which he did not know. He has always been worrisome and nervous and was frequently disturbed in his sleep by dreams and marked irritability.

In 1944, about five years before I first saw him, he was awakened one night by severe cramps in the anterior part of the chest and severe pain radiating to the lower jaw, lasting 15 to 20 minutes. These pains recurred spontaneously on and off over a period of five years, although at times he was free from the attacks for several months at a time. He continued his work without interruption during the entire five years. The pain at no time was related to any exertion. He was treated by a doctor who told him they were "nerve spasms."

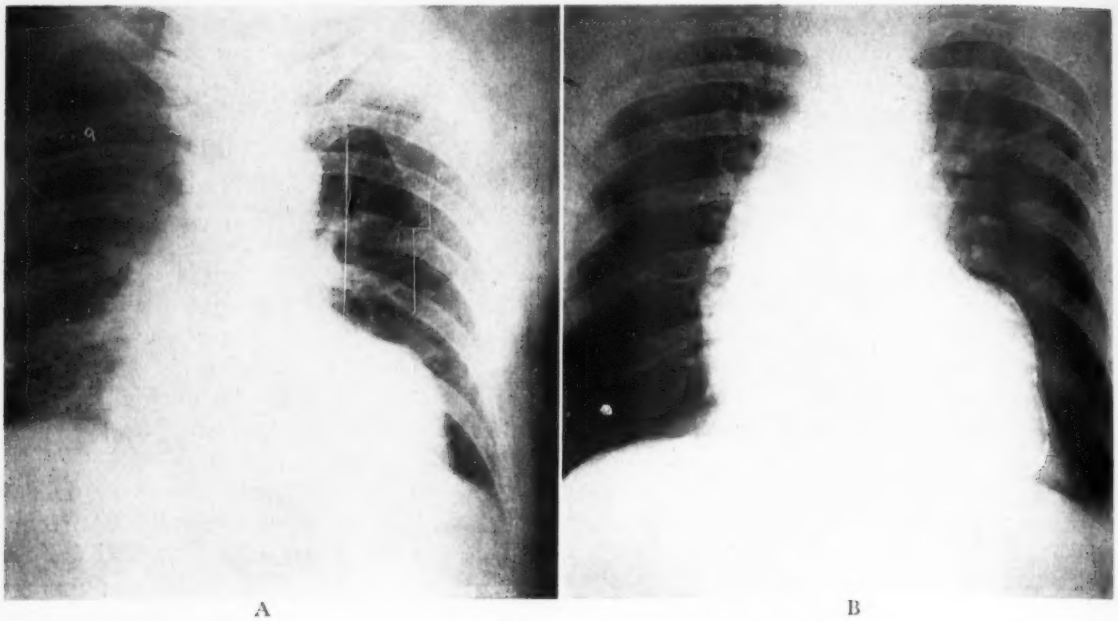
On January 24, 1949 at 11 a.m. while standing on the street he developed severe burning pain across the anterior chest which became progressively worse the rest of the day. At 5 p.m. the pain became unbearable and continued through the night, associated with cold perspiration and fainting sensation. He was removed to the Kings County Hospital. I examined him in that hospital for the first time on January 27, 1949, three days after the onset. I found him to be acutely and critically ill. His temperature was about 103; pulse about 135 and 140, very poor quality, and respiration 30. He had considerable dyspnea and a moderate ashen pallor. The heart percussed enlarged to the left and on palpation of the left precordial region, above the apex, a forward systolic thrust was felt synchronous with apical retraction. The electrocardiogram showed anterolateral left ventricular wall infarction. My impression was that he had acute myocardial infarction and had developed an aneurysm at the site of the infarct. A bedside x-ray of the chest the following day revealed a tumefaction in the region of the left border of the heart which the roentgenologist interpreted as an extrinsic tumor close to the heart. He was of the opinion that an aneurysm of the heart could not have developed so soon after the onset of myocardial infarction.

The patient ran a very stormy course in the hospital with a fluctuating temperature of 101 to 103, recurring severe chest pain and cardiac failure.

At the end of six weeks he recovered well enough to be sent home. Before discharge the roentgenologist did a teleoroentgenogram and a fluoroscopic examination of the chest and confirmed the diagnosis of aneurysm of the anterior wall of the left ventricle.

Subsequent Course: Since his discharge from the hospital, a period of over nine years, he has been and still is under my observation. The first few weeks after his discharge he had recurring attacks of left heart failure with pulmonary edema. The temperature varied between 100 and 102, pulse 110 to 130 at different times, respiration 25 to 30. The heart sounds were of poor quality. A faint systolic murmur was heard at the apex from time to time and there was evidence suggestive of embolization to the kidney and spleen. Under digitalization, anticoagulant therapy, mercurial diuretics and good nursing the condition finally became quiescent.

I have examined him on numerous occasions since then. He complained from time to time of recurring pain in the left lower precordial region, some dyspnea and choking sensation, palpitation and various other disturbances. During the first two years of my observation he frequently showed evidence of recurring left heart failure which ultimately subsided. The lungs remained persistently clear. The heart rate varied between 90 and 110 on various occasions. The heart sounds which were diminished in intensity at first, gradually returned to normal and later the first sound and the second aortic sound became accentuated. The faint systolic murmur heard the first two months has subsided and no murmur has been heard since then. The blood pressure in the first year varied between 140 and 155 systolic and 90 and 100 diastolic. As time went on it slowly began to mount, so that lately it varies between 155 and 190 systolic and 100 to 120 diastolic at various times. There is also some acceleration of the heart rate to as high as 130 per minute at times when he is excited, although most of the time it is in the neighborhood of 90 to 100.



A

Fig. 1A. Teleoroentgenogram about six weeks after onset of infarction, similar to one obtained soon after infarction. Large aneurysmal bulge upper anterior wall, left ventricle.

B

Fig. 1B. Eight and one-half years later. The previous and an additional aneurysm are seen with linear calcification of both.

Of late he has been complaining from time to time of dizziness, weakness, burning pain in the anterior chest radiating to the lower jaw, a sense of "paralysis" of both arms, faintness, nausea, and other subjective disturbances, many of which cannot be traced to his cardiac pathology. His symptoms are greatly diminished after reassurance. He experiences some anginal pain on moderate exertion. He does some work about the house and often takes long walks without discomfort.

X-ray and Electrocardiographic Findings: Several roentgenologic examinations of the chest were done and many electrocardiograms were obtained to date during the period of over nine years of observation. Figure 1A is a teleoroentgenogram obtained soon after discharge from the hospital, that is, about six weeks after the onset of infarction. It appears the same as the one obtained in the hospital soon after the onset of the infarction. It shows a large aneurysm of the upper anterior wall of the left ventricle. Figure 1B was obtained eight and one-half years later. It shows the original aneurysm in the same location and in addition there is a smaller aneurysm at the apical portion of the left ventricle, demonstrated on deep inspiration. This second aneurysm developed gradually during the first year following the attack of myocardial infarction. Both aneurysms are clearly outlined by a linear calcified streak covering the outer left border of the heart.

Figure 2 shows three electrocardiograms selected out of a series of twenty obtained over a period of nine years. Figure 2A was obtained about three months after the onset of myocardial infarction. The outstanding features are the presence of a QS wave with persistent elevation of the QS-T segment in leads I, aVL, V_4, V_5 and V_6 and some depression of the R-T segment in leads II, III, and aVF. The T wave is negative in leads I, II, V_4, V_5, and V_6. All these features were present in the early phase of infarction.

Figure 2B was obtained two and one-half years after 2A. This tracing still shows some elevation of the QS-T segment in leads I, aVL, V_4, V_5 and V_6 although slightly less than in 2A and there is slight depression of the R-T segment in leads II, III and aVF. The T wave in leads V_4, V_5 and V_6 is not as negative as before and it has a diphasic tendency in

V_4. The QRS complex in lead I is now of much lower voltage and a vestigial R wave is appearing.

Figure 2C was obtained recently, about nine years after the attack. At this time there is noted a well defined R wave with a somewhat greater elevation of the R-T segment in leads I, aVL, and V_6. The elevation of the QS-T segment in leads V_4 and V_5 remains the same but the T wave in those leads is definitely diphasic, the negative phase being less prominent than before. These findings indicate considerable improvement in the depolarization and repolarization in the anterolateral wall of the left ventricle.

Comments

The interesting features in this case are: (1) the very early appearance of an aneurysm in the left ventricle in the course of acute myocardial infarction; (2) the development of a second aneurysm in the same ventricle lower down over a period of the two years following the infarction; (3) the great longevity of the patient, now over nine years since the attack of infarction which caused the aneurysm; (4) the relatively good functional capacity of the heart; (5) the freedom from acute recurrences of infarction; (6) the absence of embolization from the possible presence of mural thrombi in the aneurysmal sac, after the early subacute phases of the disease subsided; (7) the linear calcification of the aneurysms at the pericardial surface which outlines and more or less separates the two aneurysmal areas; and, (8) no recurrence of left heart failure, in spite of the fact that there has been a somewhat mounting systolic arterial blood pressure for the past few years.

This case illustrates the fact that once complete organization of damage due to infarction occurs, and no recurrence of infarction takes place, the prognosis is good no matter how severe the original damage might have been. It also points to the fact that embolization from possible mural thrombi in an aneurysmal cavity will occur only when the process is still in the

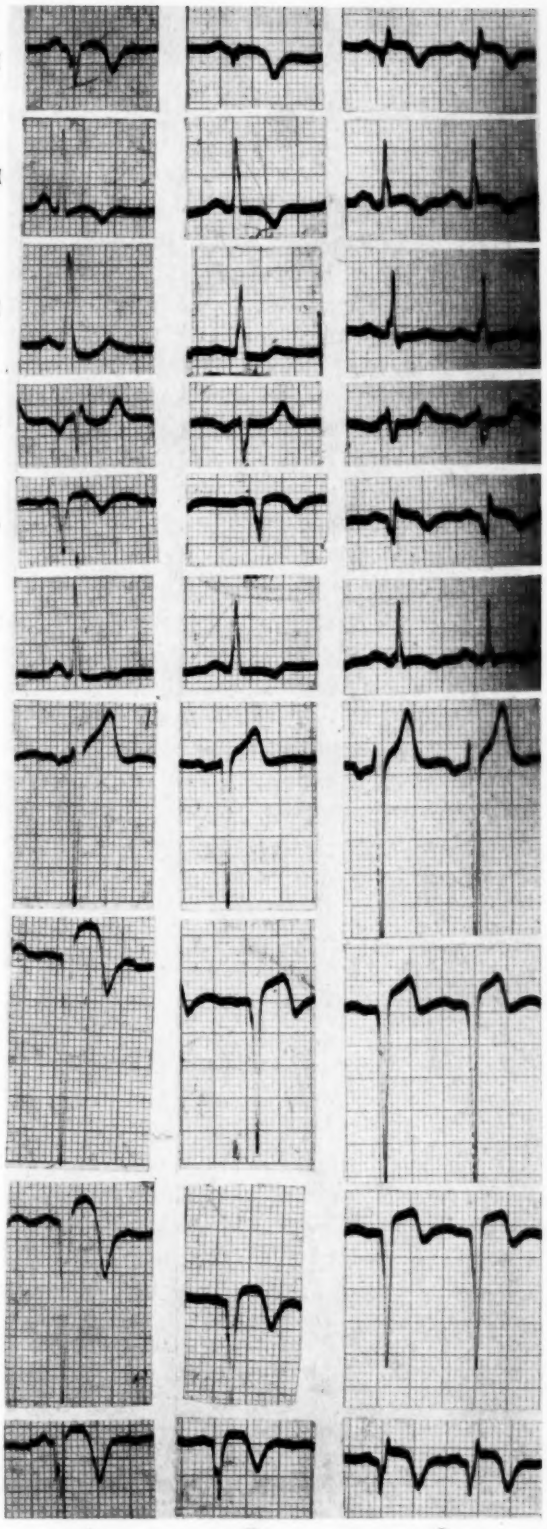


Fig. 2. (A) Electrocardiogram three months after onset of infarction; (B) two and one-half years later; (C) nine years after the attack. For description see text.

acute and subacute phases of the disease. Once complete organization of thrombi occurs the probability is that no further thrombosis within the aneurysmal cavity will develop, even though theoretically it would be expected to occur.

Summary

Aneurysm of the heart following myocardial infarction is not infrequent at autopsy, but its diagnosis during life is often missed. It may affect the anterior or the posterior wall of the left ventricle or the interventricular septum. It very rarely develops during the phase of infarction and longevity is relatively short. No more than about 12 per cent of cases live longer than five years.

The case reported here developed physical signs and roentgenologic findings of aneurysm of the upper anterior part of the left ventricle three days after the onset of infarction and at the present writing, more than nine years later, the patient is still alive and shows fairly good cardiac function. A second aneurysm developed at the apical portion within two years after the same infarction. Calcification involving both aneurysms took place. There was no recurring infarction, no embolization and no heart failure after the subacute phase of the disease subsided.

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Historical Milestones

William Harvey Described by an Eyewitness (John Aubrey)

SAUL JARCHO, M.D.

New York, New York

WE ARE accustomed to think of the great personages of the past as noble statuesque figures—perfect, virtuous, and generally devoid of credible human characteristics. We imagine Hippocrates as a bearded, benign, immobile immortal (like the bust in the New York Academy of Medicine), an ideal physician who could never have been exasperated by a patient's relatives. As for the Romans, we tend to imagine that they were mostly made of marble, except of course for Cleopatra, and she was not a Roman but an Egyptian, although she intruded notoriously on the history of Rome.

In view of our inveterate tendency to deify the great, we are startled and delighted to come upon a lifelike description of a famous person, depicted with his foibles as well as his virtues. It is the further good fortune of readers of THE AMERICAN JOURNAL of CARDIOLOGY that this famous person is the founder of their art, William Harvey (1578–1657).

John Aubrey, the author of the description which is excerpted here, was an antiquarian, a gossip and a scatterbrain. The designation "scatterbrain" indicates clearly enough the presence of cranial contents but also describes the dearth of persistence which made it difficult for Aubrey, despite great ability, to complete any extensive or systematic piece of writing. His restless curiosity constantly sought him to seek information and to jot down brief notes, while the scope of his interests included human nature, antiquities, and natural history. From the morass of Aubrey's heavily interlined and almost illegible manuscripts, Mr. Oliver Lawson Dick with exemplary patience succeeded in disinterring 426 biographical notices, of which he deemed 134 worthy of publication. Mr. Dick's volume was published in London in 1950 by Messrs. Secker and Warburg. I am indebted to the University of Michigan Press, holder of the American publication rights, for gracious permission to use the following excerpts.

The reader who consults Mr. Dick's book will be happy to find in it vivid biographies and descriptions of such men as Francis Bacon, Richard Boyle, Sir Edward Coke, Ben Jonson, John Milton, William Shakespeare, and many others.

EXCERPTS FROM JOHN AUBREY'S LIFE OF WILLIAM HARVEY

WILLIAM HARVEY, Dr. of Physique and Chirurgery, Inventor of the Circulation of the Bloud, was borne at the house which is now the Post-house, a faire stone-built-house, which he gave to Caius college in Cambridge, with some lands there. His brother Eliab would have given any money or exchange for it, because 'twas his father's, and they all borne there; but the Doctor (truly) thought his memory would better be preserved this way, for his brother has left noble seates, and about 3000 pounds per annum, at least.

William Harvey, was always very contemplative, and the first that I heare of that was curious in Anatomie in England. I remember I have heard him say he wrote a booke *De Insectis*, which he had been many yeares about,

and had made dissections of Frogges, Toades, and a number of other Animals, and had made curious Observations on them, which papers, together with his goods, in his Lodgings at Whitehall, were plundered at the beginning of the Rebellion, he being for the King, and with him at Oxon; but he often sayd, That of all the losses he sustained, no griefe was so crucifying to him as the losse of these papers, which for love or money he could never retrive or obtaine.

When Charles I by reason of the Tumults left London, he attended him, and was at the fight of Edge-hill with him; and during the fight, the Prince and Duke of Yorke were committed to his care. He told me that he withdrew with them under a hedge, and tooke out of his pockett a booke and read; but he had not read very long before a Bullet of a great Gun grazed on the ground neare him, which made him remove his station. . . .

I first sawe him at Oxford, 1642, after Edgehill fight, but was then too young to be acquainted with so great a Doctor. I remember he came severall times to Trinity College to George Bathurst, B.D., who had a Hen to hatch Egges in his chamber, which they dayly opened to discerne the progres and way of Generation. I had not the honour to be acquainted with him till 1651, being my she cosen Montague's physitian and friend. I was at that time bound for Italy (but to my great griefe disswaded by my mother's importunity). He was very communicative, and willing to instruct any that were modest and respectfull to him. And in order to my Journey, gave me, i.e. dictated to me, what to see, what company to keepe, what Bookes to read, how to manage my Studies: in short, he bid me go to the Fountain head, and read Aristotle, Cicero, Avicenna, and did call the Neoteriques shitt-breeches.

He wrote a very bad hand, which (with use) I could pretty well read. He understood Greek and Latin pretty well, but was no Critique, and he wrote very bad Latin. The *Circuitis Sanguinis* [Circulation of the Blood] was, as I take it, donne into Latin by Sir George Ent. . . .

His Majestie King Charles I gave him the Wardenship of Merton Colledge in Oxford, as a reward for his service, but the Times suffered him not to recieve or injoy any benefitt by it.

After Oxford was surrendred, which was 24, July, 1646, he came to London, and lived with his brother Eliab a rich Merchant in London, who bought, about 1654, Cockaine-house, now (1680) the Excise-office, a noble house, where the Doctor was wont to contemplate on the Leads of the house, and had his severall stations, in regard of the sun, or wind.

He did delight to be in the darke, and told me he could then best contemplate. He had a house heretofore at Combe, in Surrey, a good aire and prospect, where he had Caves made in the Earth, in which in Summer time he delighted to meditate.

Ah! my old Friend Dr. Harvey—I knew him right well. He made me sitt by him 2 or 3 hours together in his meditating apartment discoursing. Why, had he been stiffe, starcht, and retired, as other formall Doctors are, he had known no more than they. From the meanest person, in some way, or other, the learnedst man may learn something. Pride has been one of the greatest stoppers of the Advancement of Learning.

He was far from Bigotry.

He was wont to say that man was but a great, mischievous Baboon.

He had been physitian to the Lord Chancellour Bacon, whom he esteemed much for his witt and style, but would not allow him to be a great Philosopher. Said he to me, *He writes Philosophy like a Lord Chancellor*, speaking in derision; *I have cured him*. . . .

He would say that we Europeans knew not how to order or governe our Woemen, and that the Turks were the only people used them wisely.

I remember he kept a pretty young wench to wayte on him, which I guesse he made use of for warmeth-sake as King David did, and tooke care of her in his Will, as also of his man servant.

He was very Cholerique; and in his young days wore a dagger (as the fashion then was) but this Dr. would be to apt to draw-out his dagger upon every slight occasion.

I have heard him say, that after his Booke of the *Circulation of the Blood* came-out, that he fell mightily in his Practize, and that 'twas beleeved by the vulgar that he was crackbrained; and all the Physitians were against his Opinion, and

envyed him; many wrote against him. With much adoe at last, in about 20 or 30 yeares time, it was recieved in all the Universities in the world; and, as Mr. Hobbes sayes in his book *De Corpore, he is the only man, perhaps, that ever lived to see his owne Doctrine established in his life-time.*

He was Physitian, and a great Favorite of the Lord High Marshall of England, Thomas Howard Earle of Arundel and Surrey, with whom he travelled as his Physitian in his Ambassade to the Emperor at Vienna. In his Voyage, he would still be making of excursions into the Woods, makeing Observations of strange Trees, and plants, earths, etc., naturalls, and sometimes like to be lost, so that my Lord Ambassador would be really angry with him, for there was not only danger of Thieves, but also of wild beasts.

He was much and often troubled with the Gowte, and his way of Cure was thus; he would then sitt with his Legges bare, if it were a Frost, on the leads of Cockaine-house, putt them into a payle of water, till he was almost dead with cold, and betake himself to his Stove, and so 'twas gone.

He was hott-headed, and his thoughts working would many times keepe him from sleepinge; he told me that then his way was to rise out of his Bed and walke about his Chamber in his Shirt till he was pretty coole, i.e. till he began to have a horror, and then returne to bed, and sleepe very comfortably.

He was not tall; but of the lowest stature, round faced, olivaster complexion; little Eie, round, very black, full of spirit; his haire was black as a Raven, but quite white 20 yeares before he dyed.

I remember he was wont to drinke Coffee; which he and his brother Eliab did, before Coffee-houses were in fashion in London.

His practice was not very great towards his later end; he declined it, unlesse to a speciall friend, e.g. my Lady Howland, who had a cancer in her Breast, which he did cutt-off and seared, but at last she dyed of it. He rode on horseback with a Footcloath to visitt his Patients, his man following on foote, as the fashion then was, which was very decent, now quite discontinued. (The Judges rode also with their Foote-cloathes to Westminster-hall, which ended at the death of Sir Robert Hyde, Lord Chief Justice. Anthony Earl of Shafton, would have revived, but severall of the judges being old and ill horsemen would not agree to it.)

All his Profession would allow him to be an excellent Anatomist, but I never heard of any that admired his Therapeutique way. I knew several practisers in London that would not have given 3d. for one of his Bills [prescriptions]; and that a man could hardly tell by one of his Bills what he did aime at. (He did not care for Chymistrey, and was wont to speake against them with an undervalue.)

He had, towards his latter end, a preparation of Opium and I know not what, which he kept in his study to take, if occasion should serve, to putt him out of his paine, and which Sir Charles Scarborough promised to give him; this I beleeve to be true; but doe not at all beleeve that he really did give it him.

Not but that, had he laboured under great Paines, he had been readie enough to have donne it; I doe not deny that it was not according to his Principles upon certain occasions. But the manner of his dyeing was really, and *bona fide*, thus, viz. the morning of his death about 10 a clock, he went to speake, and found he had the dead palsey in his Tongue; then he sawe what was to become of him, he knew there was then no hopes of his recovery, so presently sends for his brother and young nephewes to come-up to him, to whom he gives one his Watch ('twas a minute watch with which he made his experiments), to another another thing, etc., as remembrances of him; made a signe to Sambroke, his Apothecary, to lett him blood in the tongue, which did little or no good; and so ended his dayes. The Palsey did give him an easy Passe-port.

For 20 yeares before he dyed he tooke no manner of care about his worldly concernes, but his brother Eliab, who was a very wise and prudent menager, ordered all not only faithfully, but better then he could have donne himselfe. He dyed worth 20,000 pounds, which he left to his brother Eliab. In his Will he left his old friend Mr. Thomas Hobbes 10 pounds as a token of his Love.

He lies buried in a Vault at Hempsted in

Essex, which his brother Eliab Harvey built; he is lapt in lead, and on his brest in great letters

DR. WILLIAM HARVEY.

I was at his Funerall, and helpt to carry him into the Vault.

COMMENT

Aubrey's brief life of Harvey is obviously a portrait rather than a biography. The many small details which the author noted not only add up to make a singularly lifelike description but also contain much that is of interest to the clinical investigator and the medical historian.

Harvey is described as contemplative but fond of informal discussion and willing to teach. He was free from bigotry but was evidently choleric and somewhat forthright in the expression of his opinions. His interest in natural history was not limited to dissection but—as all the world knows—also took expression in experiment. He was scurrilously contemptuous of recent writers and preferred Aristotle, Cicero, and Avicenna. Like many physicians who are deeply involved in research, he was an indifferent practitioner and did not excel in therapeutics.

After Harvey's discovery of the circulation was published "he fell mightly in his Practize." His work met widespread opposition, which gradually subsided. Recognition came during his lifetime.

Such was William Harvey. Those who seek to follow in his footsteps would do well to consider the path.

A-V Block Due to Digitalis Intoxication

HISTORY

THIS 68-year-old white male* had been complaining of exertional precordial pain for five years (since 1952). He had had a myocardial infarction in 1943 and had been suffering from intermittent claudication for several years. He was now complaining of epigastric pain, radiating to the right hypochondrium and accompanied by oppression. This pain occurred from time to time without apparent cause, but lasted only a few minutes. He was an excitable man and a heavy smoker. The patient had been taking digitoxin since 1956.

CLINICAL FINDINGS

Physical examination revealed a regular pulse of 52 which, however, was interrupted every 5 to 6 beats by a premature contraction. Blood pressure was 280/80. The heart was of normal size and configuration. There were no thrills or murmurs but a muffled 1st sound was heard at the apex. The liver was palpable (one finger) and tender.

An electrocardiogram revealed sinus rhythm and occasional ventricular extrasystoles; no evidence of the old infarct.

On 10/29/57, more severe attacks of epigastric and right hypochondrial pain occurred. They usually took place after meals and were followed by vomiting. Examination at this time revealed a regular pulse of 40, with occasional premature contractions, and blood pressure of 160/80.

An electrocardiogram was taken (Fig. 1A). This revealed complete A-V block and extremely slow atrial rhythm, so that the atrial and ventricular beats had nearly the same rate (ventricular = 40; atrial = 38). The diagnosis of *double rhythm and complete A-V block* was made.

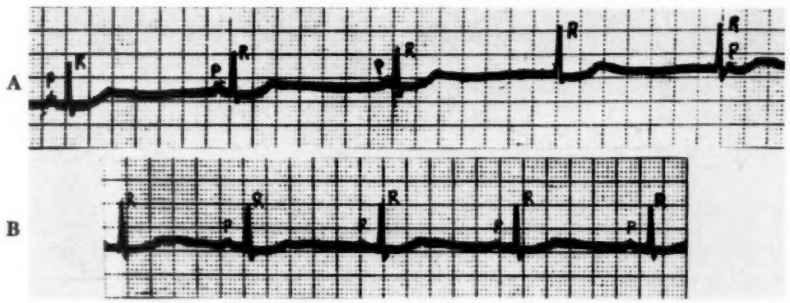

Fig. 1A. Electrocardiogram in Lead 2, recorded on 12/15/57. Double rhythm with complete A-V block. (B) Electrocardiogram in Lead 2, recorded on 1/10/58. Sinus rhythm with normal A-V conduction.

DISCUSSION

At this point, several possibilities were discussed: (a) myocardial infarct with A-V block; (b) A-V block in a coronary heart patient without infarct; (3) digitalis intoxication causing A-V block. The last diagnosis was considered the most likely and digitoxin was discontinued.

A new electrocardiogram was recorded two weeks later (Fig. 1B). Sinus rhythm had been

* Case of Dr. P. Ravenna.

resumed. This confirmed the accuracy of the diagnosis.

Complete A-V block can be produced in animals following intensive digitalization. In man, digitalis is listed as a possible cause of complete A-V block, but such an occurrence is rare. It should be considered that lasting complete A-V block following digitalization occurs only if there already is a lesion of the conducting tissues, so that the drug acts on damaged cells, thus obtaining a greater effect. Usually, the atrial rate in complete A-V block is normal. The extremely marked slow rate of this case can be explained by the vagal stimulation and the myocardial effect on the S-A node produced by digitalis.

A. A. Luisada, M.D.
A. Jacono, M.D.
Chicago, Illinois

Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

Investigators and research workers are invited to submit, with a view to publication in an early issue, résumés of work in progress or recently completed.

Renal Lesions Accompanying Potassium Deficiency

A SPECIFIC renal lesion characterized by hydropic tubular change is observed occasionally in a wide variety of conditions which have chronic potassium deficiency.[1–3] Clinically, this lesion is accompanied by severe symptoms and findings of renal tubular failure, including hyposthenuria, which persist for some time after the blood potassium level has been restored to normal.

Therefore, Drs. W. N. Tauxe, K. G. Wakim and A. H. Baggenstoss[4] (Mayo Clinic) attempted to produce the disease in weanling rats by potassium dietary restriction. When symptoms became severe, potassium was restored to the diet and the pattern of the regression of the lesions was observed. Suitable controls were used to rule out the effects of compensatory hypertrophy and the possibility of inadequacy of other dietary elements. Except for potassium, the synthetic diet seemed to be as nourishing as the regular ration.

Renal lesions similar to those observed in chronic potassium deficiency in man were produced in rats by withholding potassium from their diets. These lesions differed quantitatively from those in man in that the degree of vacuolation is more intense in man.

Profound disturbances of growth were produced. During the first two weeks of the study, the control animals gained an average of 74 g, more than doubling their initial weights. The potassium-deficient animals gained only 6 g, a tenth of their initial weights. However, the kidney weights of the potassium-deficient rats exceeded that of the controls in spite of the fact that their body weights were much less.

A distinctive lesion involving the entire nephron was produced. It consisted of dilatation of the tubules with necrosis of parenchyma and vacuolation of the cytoplasm. The lesion progressed in severity from the glomerulus to distal collecting tubules.

On restoration of potassium to the diet, it was found that the lesions disappeared in order of severity, that is, from glomerulus to distal collecting tubule, and that approximately three weeks was required for this process. This finding parallels clinical observations in man. Since this lesion in man probably has produced death due to renal failure, it seems wise to suspect its presence in renal failure associated with potassium deficiency, especially since the lesion appears to be reversible.

At the Mayo Clinic[2] such a renal lesion has been observed in association usually with intestinal diseases accompanied by diarrhea. Others[5] have reported it in the diarrhea of chronic laxative overdosage in compulsion neurosis.

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Postmortem Study of the Technic of Aortic Valvulotomy by Examination of Valvular Function

During the past two years, Drs. W. Gerald Austen, Robert S. Shaw, J. Gordon Scannell, and W. M. Thurlbeck (Massachusetts General Hospital) studied the hearts of 36 patients who died with severe aortic stenosis, by perfusing the aortic valve and quantitatively determining the degree of aortic stenosis and regurgitation. These valves were then restudied after various reconstructive procedures had been performed on them.

The following observations were made:

(1) Closed (blind) commissurotomy or dilatation usually resulted in a forbidding degree of regurgitation and inconsistent relief of stenosis, with frequent release of gross calcareous emboli.

(2) It was possible to consistently relieve stenosis without significant resultant regurgitation and without the uncontrolled release of calcareous emboli by debridement and commissurotomy under direct vision.

(3) Accurate identification of the commissure is the key to successful commissurotomy. This can be accomplished by: (a) initial debridement and observation of the regions of fusion, and (b) determination of the junction of the commissure with the aortic wall by its distal position in the aorta, and by the presence of a thickening at this point on the aortic wall.

(4) Inspection of normally functioning valves and experimental experience have shown that the commissure can be normally fused in its first 2 mm and that division of diseased commissures beyond this point and to the aortic wall, affords no decrease in valvular resistance to forward flow, but does frequently increase regurgitation.

(5) Division of two out of three commissures resulted in persistent moderate stenosis. Division of the third commissure uniformly relieved this stenosis and occasionally even decreased regurgitation.

Bicuspid valves were encountered. Failure to recognize this entity, and artificial construction of a third commissure resulted in free regurgitation. Satisfactory relief of stenosis was accomplished by division of the two commissures in the usual manner.

Did you know that . . .

Rheumatic fever is apparently more common in patients with atrial septal defects (ostium secundum lesions) than in other congenital cardiac patients. However, subacute bacterial endocarditis is extremely rare in atrial septal defect patients, whereas it is relatively common in the other congenital cardiac abnormalities. (It is also relatively common in atrial septal defects due to a persistent ostium primum.)

* * *

The electrocardiogram of a patient with atrial septal defect usually shows right bundle branch block rather than the usual pattern of right ventricular hypertrophy. (A similar electrocardiographic pattern occurs in Ebstein's abnormality.)

* * *

Cyanosis precedes clubbing in congenital heart disease. Therefore, if clubbing is present without cyanosis, congenital heart disease is probably not the cause of the clubbing.

* * *

In an infant, localized cyanosis of the body above the brim of the pelvis occurs with transposition of the great vessels, in association with a patent ductus arteriosus. Local cyanosis below the brim of the pelvis in an infant occurs with an absent aortic arch, an infantile type of coarctation of the aorta (with a patent ductus arteriosus), or with a patent ductus arteriosus associated with pulmonary hypertension and a right-to-left shunt through the ductus.

The best way to see such local cyanosis in an infant is to place the hand next to the foot.

E. G.

The Query Corner

READERS are invited to submit queries on all aspects of cardiovascular diseases. Insofar as possible these will be answered in this column by competent authorities. The replies will not necessarily represent the opinions of the American College of Cardiology, the JOURNAL or any medical organization or group, unless stated. Anonymous communications and queries on postcards will not be answered. Every letter must contain the writer's name and address, but these will not be published.

Electrocardiogram in "Silent" Infarcts

Query: What types of myocardial infarction are most likely to be "silent" electrocardiographically?

Answer: There are certain regions of the myocardium which, when dead, may not cause recognizable changes in the standard electrocardiogram. These areas include: The high posterior and high lateral walls of the left ventricle, the septum, the entire right ventricle, the apex, and the auricles.

Multiple small infarctions and small anterior or intramural infarctions also may not be apparent. A lesion limited to the septum will not necessarily produce electrocardiographic changes which can be interpreted as evidence of myocardial infarction. Such septal infarcts may produce arrhythmias such as AV block, bundle branch blocks, etc., but these findings cannot be considered as evidence of myocardial necrosis.

Furthermore, an infarct located in the high posterior wall of the left ventricle does not necessarily produce QRS changes of infarction in the standard 12 leads. This is especially true in a vertical heart, which has undergone a clockwise rotation in which the resultant electrical forces derived from this area are, in this condition, directed largely perpendicular to the frontal plane. Esophageal leads may be helpful in this kind of infarct.

The same thing occurs with an infarct involving the superior portion of the lateral wall of the left ventricle. An infarct in this area may be missed unless precordial leads are taken in areas above V_4 through V_6 position. Infarcts in the right ventricle do not necessarily produce electrocardiographic changes. Sometimes variation in QRS at V_1 and V_2 may suggest this possibility. Although unusual, an auricular infarct may produce P wave changes that can be considered suggestive of auricular involvement. Small anterior, multiple or intramural infarctions do not necessarily produce electrocardiographic changes which can be considered diagnostic of coronary occlusion.

The very apex of the heart, when infarcted, may not indicate on the 12 lead trace an infarction pattern.

E. GREY DIMOND, M.D.
Kansas City, Missouri

Digitalis in Coronary Disease

Query: Is there any rationale to digitalis therapy in coronary disease with cardiac enlargement and no frank congestive failure?

Answer: If there is *no* congestive failure then there is no rationale to treating with digitalis. However, the symptoms or signs of congestive failure may be present without being "frank," such as easy fatigability, cough, hoarseness, abdominal distress, anorexia, irritability, extrasystoles, accentuation of P_2, decreased vital capacity or prolonged circulation time. Thus, in the presence of any of these or other of the less straightforward symptoms or signs, with or without the cardiac enlargement, digitalis therapy should be instituted. If some of the above symptoms are present and yet explainable as well by concomitant disease existing besides coronary disease with failure, one may be justified in digitalizing as a therapeutic test as long as close observation and evaluation of heart size, body weight, circulation time, vital capacity, and symptoms are carried out for a specific time period.

RENÉ BINE, JR., M.D.
San Francisco, Calif.

College News

1958 INTERIM MEETING

The Seventh Interim Meeting of the College will be held on Nov. 20, 21, and 22, 1958, in New Orleans at the Jung Hotel. The Scientific Sessions will be devoted to Peripheral Vascular Disease, and will include panel meetings on physiologic aspects, diagnostic methods, medical treatment, indications for surgery, and evaluation of various surgical procedures in peripheral and cerebral vascular disease.

The Convention Chairmen are:

Local Convention Committee
EDGAR HULL, *New Orleans*
General Convention Committee
SEYMOUR FISKE, *New York*
Scientific Program Committee
JOHN S. LADUE, *New York*

Make your hotel reservations early by writing directly to the Jung Hotel.

1959 ANNUAL MEETING

The Eighth Annual Meeting of the College will be held on May 25–29, 1959 inclusive at the Benjamin Franklin Hotel, Philadelphia. Dr. Robert P. Glover has been appointed Local Convention Chairman.

Call for Abstracts of Papers

Those who wish to present a paper during the Scientific Sessions of the College should send an abstract not exceeding 300 words to the Chairman of the Program Committee, Dr. John S. LaDue, 115 East 61st Street, New York 21, N. Y.

The paper should be based on original work in any field of cardiovascular disease. Abstracts must be submitted by Feb. 15, 1959.

Announcements

English Translations of Scientific Developments in the U.S.S.R and Other Soviet Orbit Countries Available

Hematology, one of the eight Russian scientific translated journals published under contract with the National Institute of Health by Pergamon Institute, 122 E 55th St., New York, New York, is now available.

Pergamon Institute, a nonprofit foundation, was recently organized for the purpose of making available to English-speaking scientists, doctors, and engineers (from all countries that are members of the United Nations), the results of scientific, technologic, and medical research and development in the Soviet Union and other countries in the Soviet orbit. Over a hundred scientists of international standing from many other countries have given their support and will supervise the affairs of the Institute.

Helpful Aids Available

The New York Heart Association announces the availability of three booklets for the sodium restricted patient entitled:

"Your 500 Milligram Sodium Diet"—Strict Sodium Restriction
"Your 1000 Milligram Sodium Diet"—Moderate Sodium Restriction
"Your Mild Sodium-Restricted Diet"

An "emergency" identification card for the protection of patients on long-term anticoagulant therapy is now available for physicians from the American Heart Association and its affiliates. The card, designed as a wallet insert, contains space for the name, address, and phone number of the individual's physician, with space to indicate the kind of anticoagulant prescribed and the patient's blood type.